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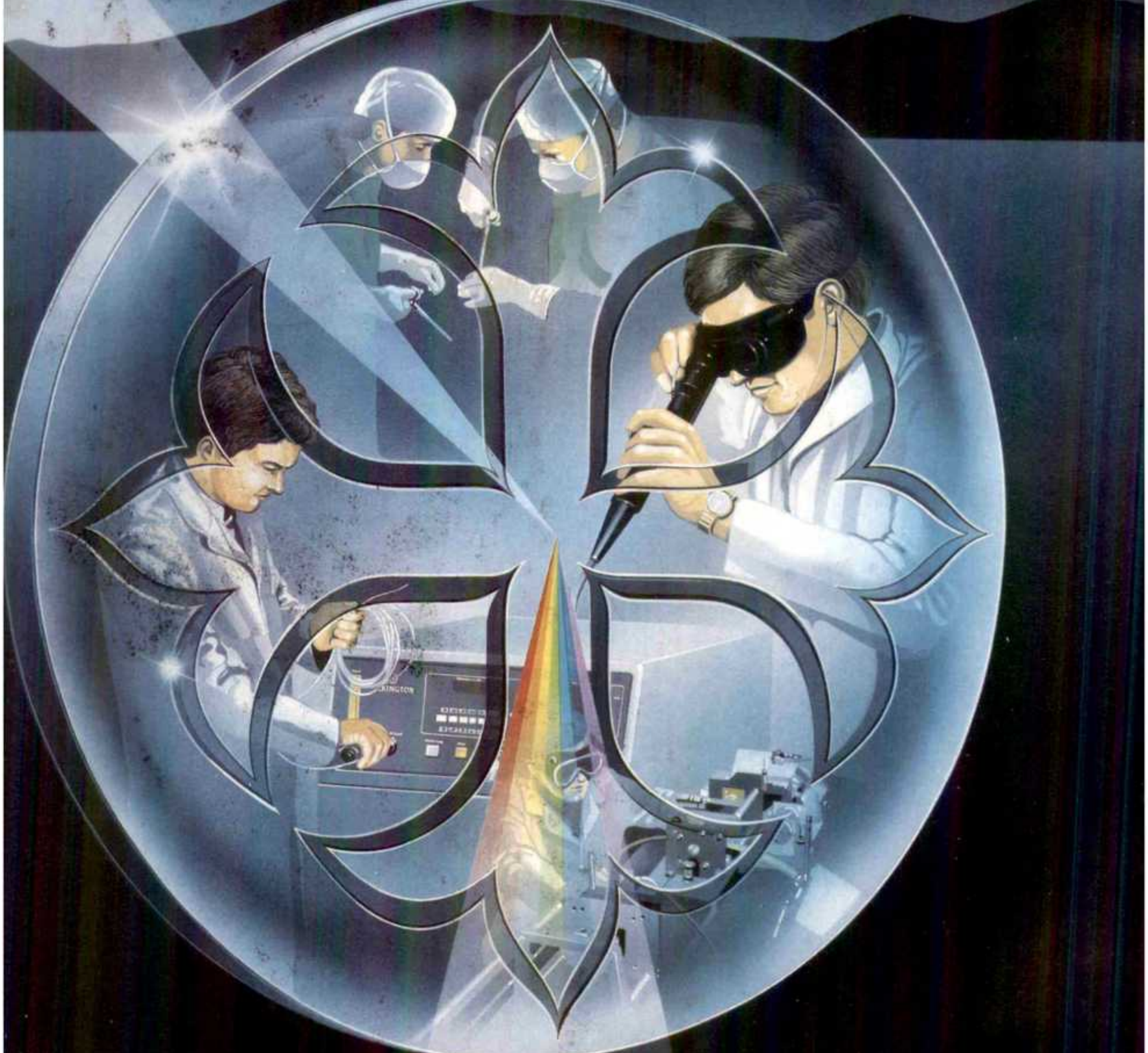

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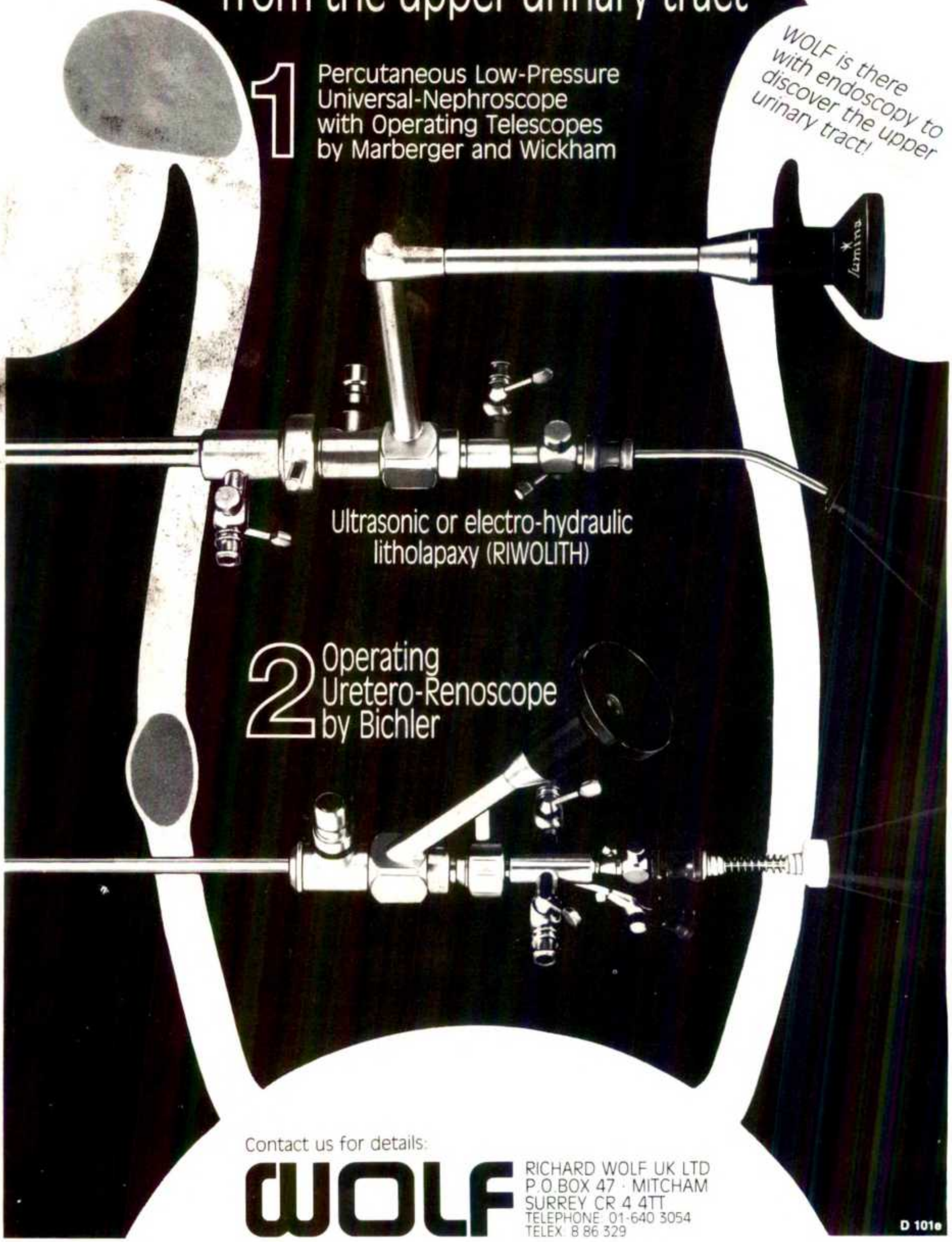
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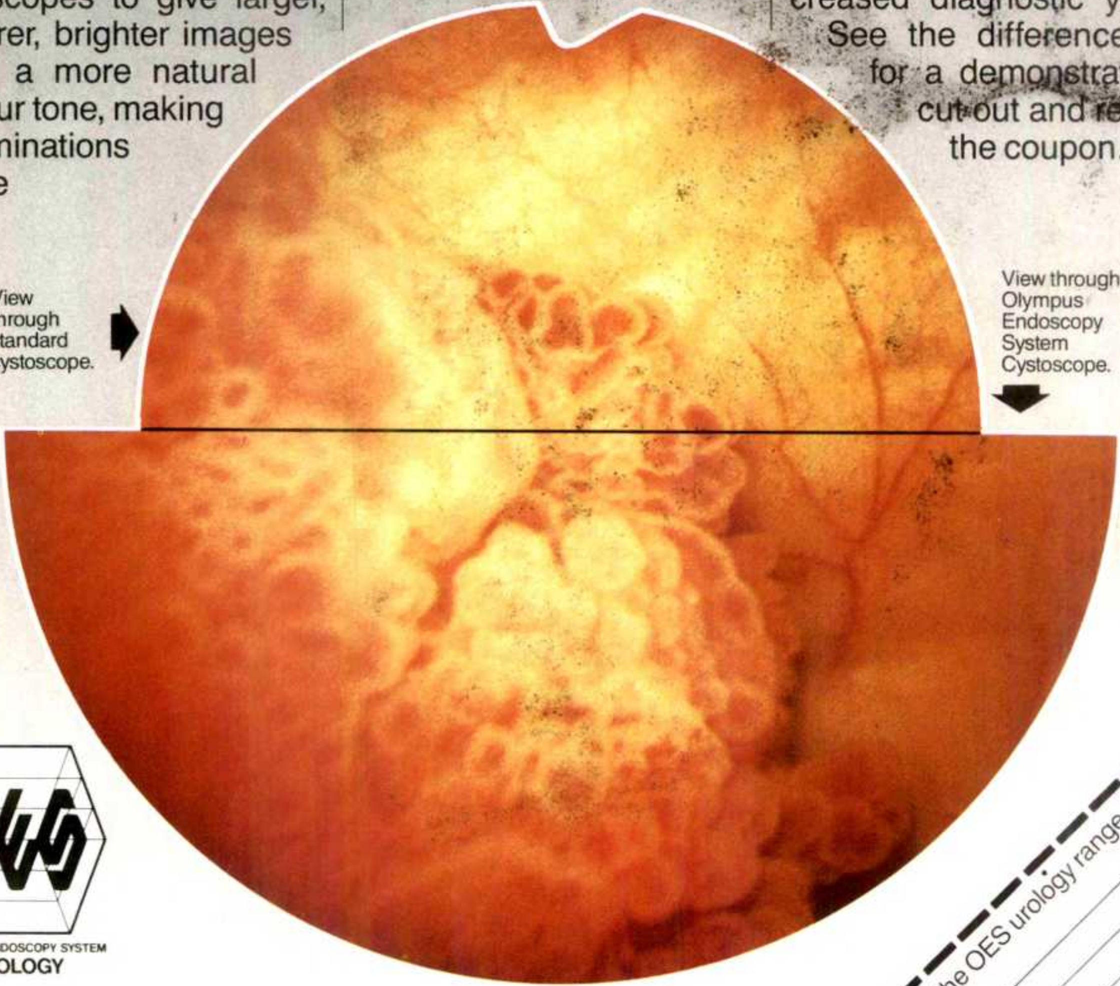
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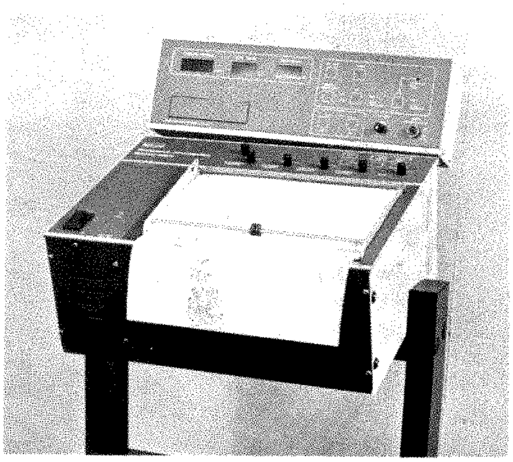

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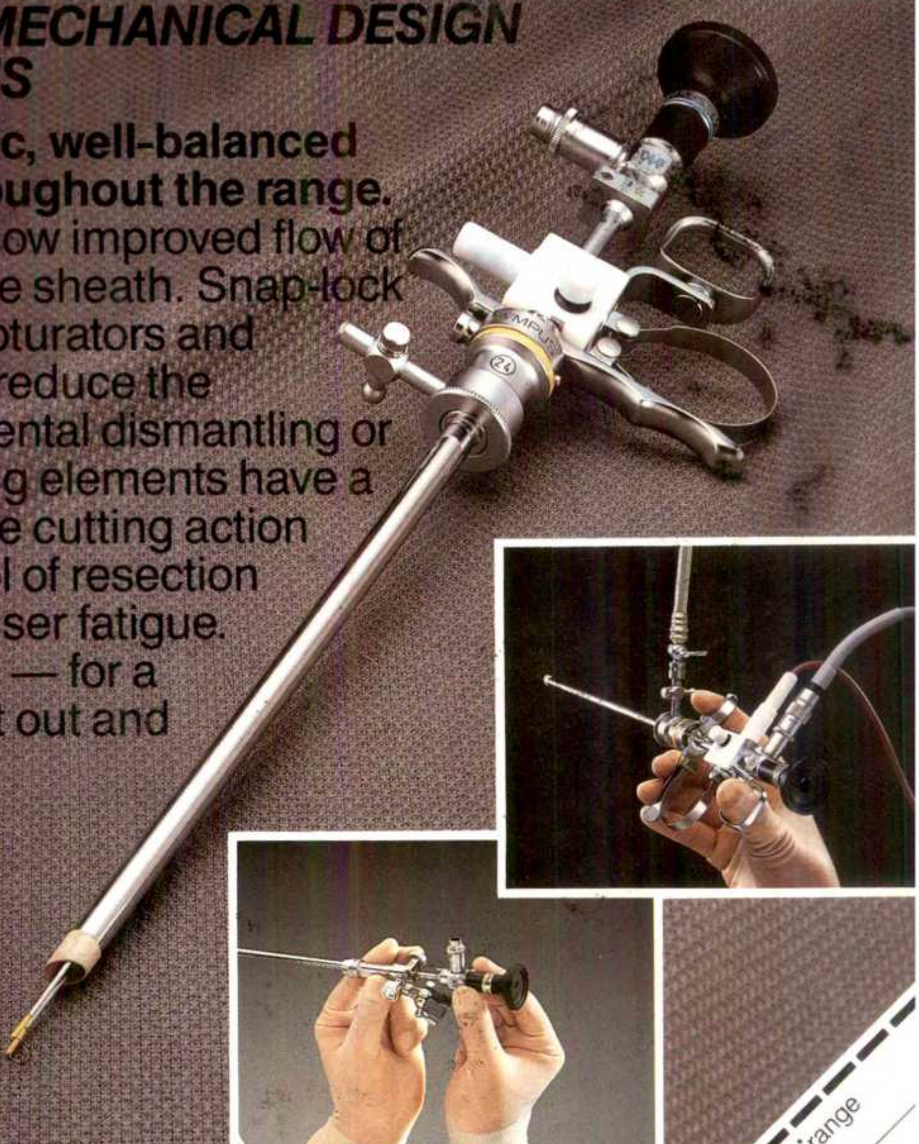

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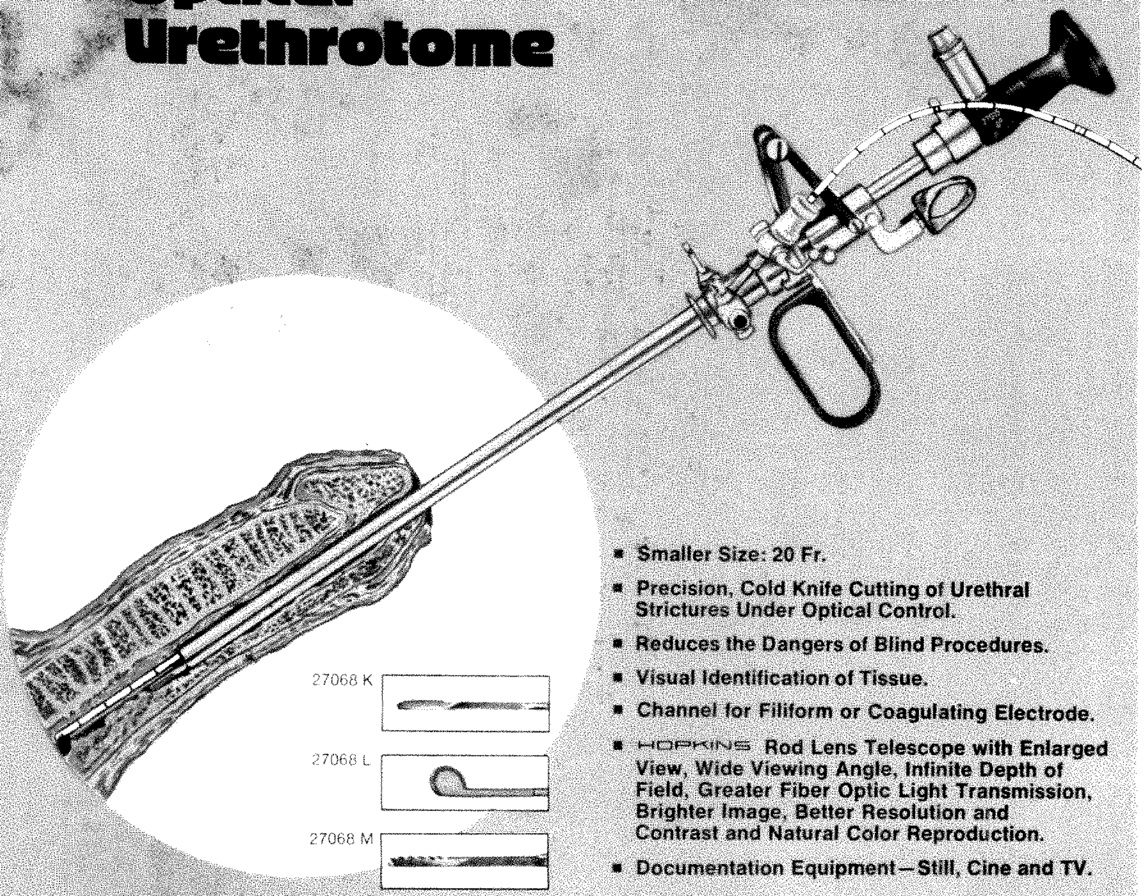

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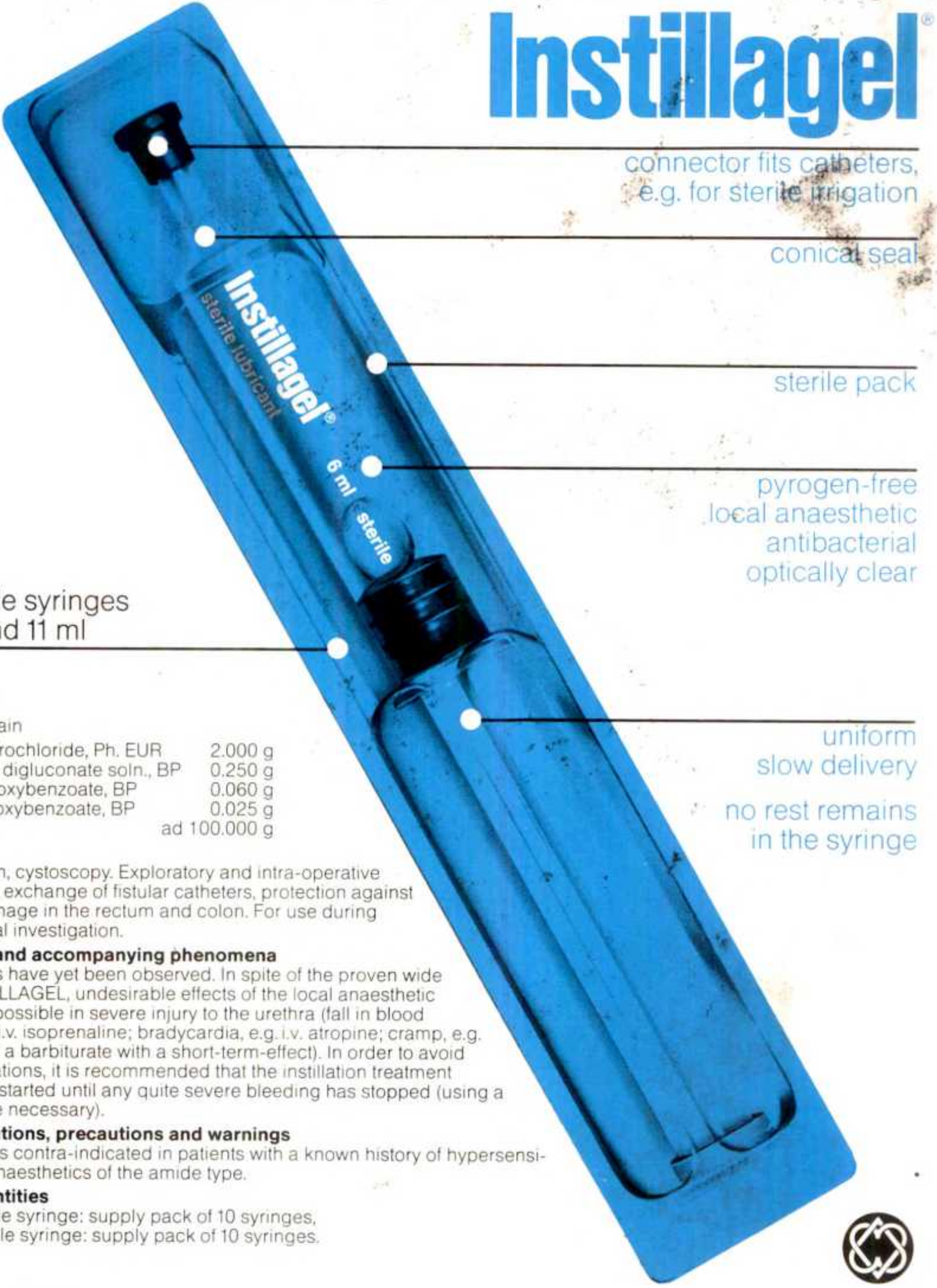

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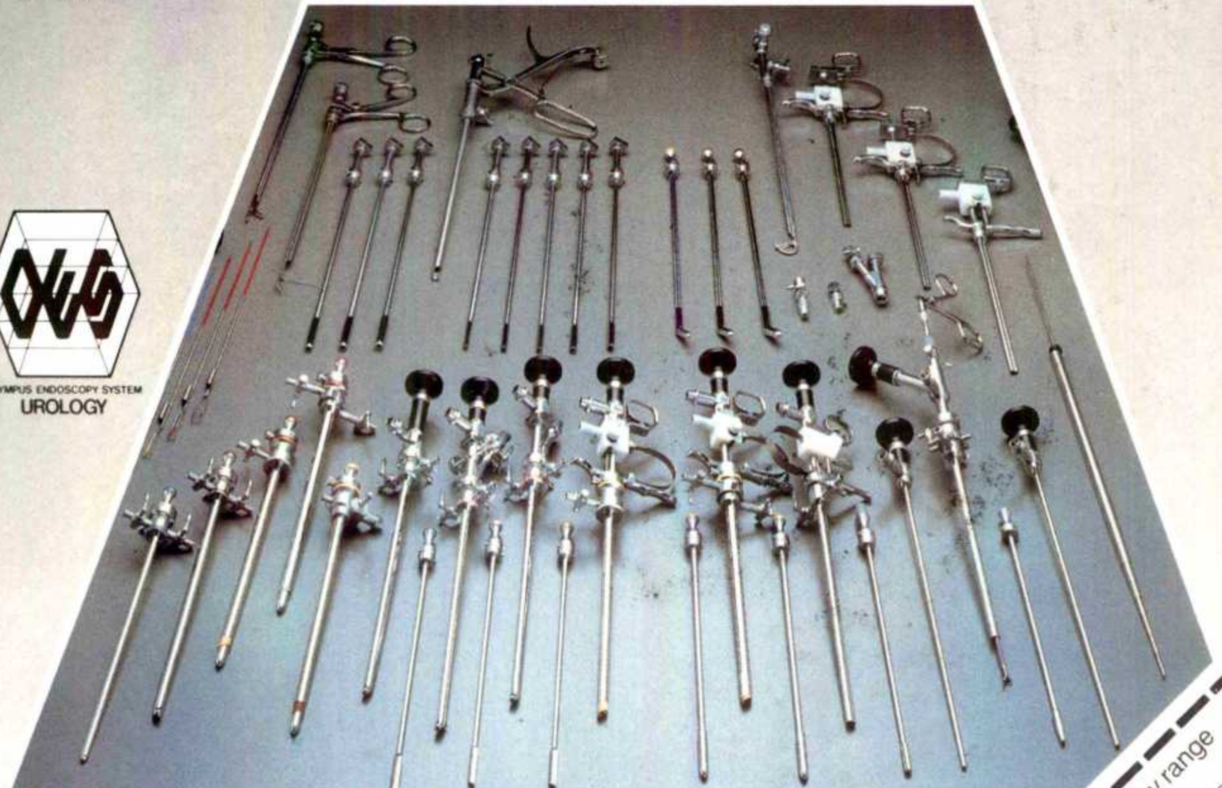

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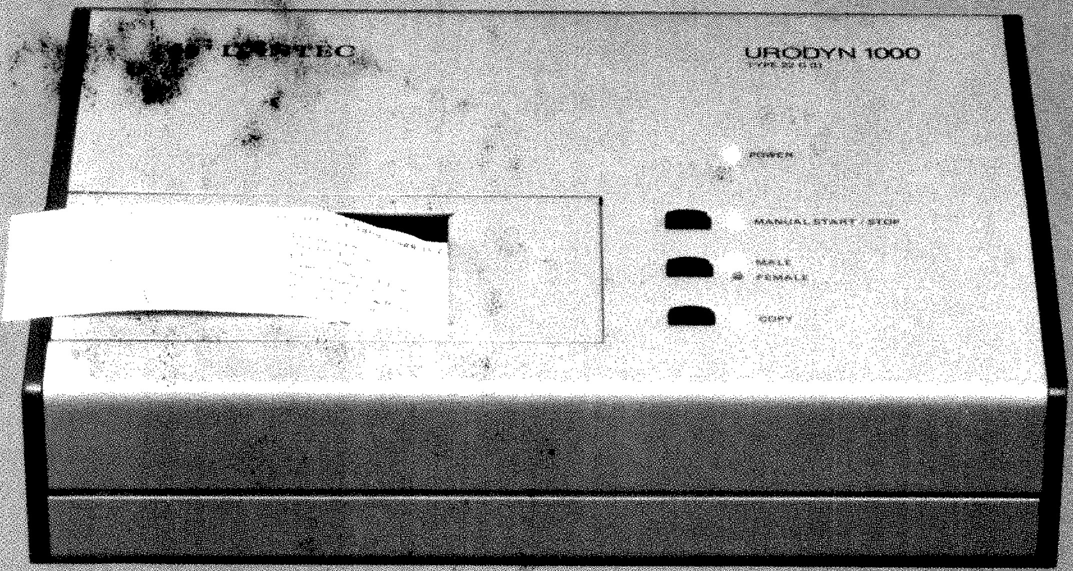

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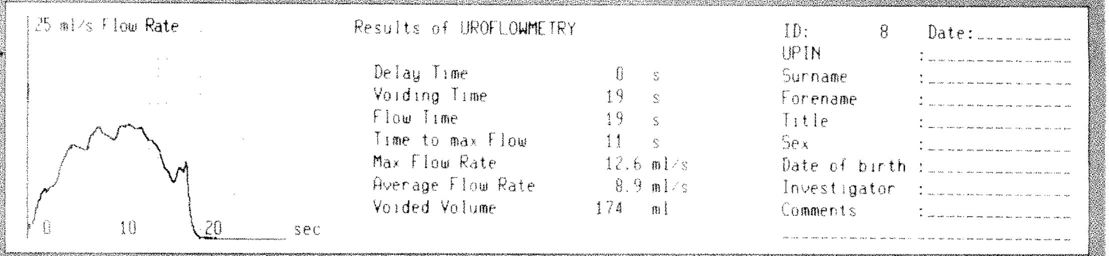

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Extracorporeal Shockwave Lithotripsy and Percutaneous Renal Surgery

Comparisons, Combinations and Conclusions

D. R. WEBB, S. R. PAYNE and J. E. A. WICKHAM

Institute of Urology and Devonshire Hospital Lithotripter Centre, London

Summary—Although percutaneous nephrolithotomy (PCNL) and extracorporeal shockwave lithotripsy (ESWL) were introduced clinically at approximately the same time (1980-1981), their clinical progress appeared to progress along separate paths and to compete with each other. After 5 years it has become apparent that for optimal removal of nearly all renal stones by minimal or non-invasive techniques, PCNL and ESWL are required either separately or as combined procedures. This review traces the development, introduction and progress of these procedures and defines the current indications for extracorporeal, percutaneous and open renal stone surgery.

Comparisons

Fernstrom and Johannson in 1976 reported three cases of basket extraction of renal calculi under image intensifier control through a nephrostomy track. However, the use of deliberate endoscopic manipulation of renal stones along these tracks was not undertaken until 1981 (Alken *et al.*, 1981; Wickham and Kellett, 1981). Chaussy *et al.* (1980) had already described the first treatments of patients by ESWL for renal and ureteric calculi. This achievement followed 8 years of laboratory and clinical research to establish the safety and effectiveness of the procedure (Chaussy, 1982). Neither percutaneous nephrostomy (PCN) nor PCNL were investigated experimentally prior to their clinical introduction, although these have been shown subsequently to have no significant effect upon renal structure or function (Webb and Fitzpatrick, 1985). Clinical follow-up has confirmed the experimental safety of both PCNL (Marberger *et al.*, 1985; Wickham *et al.*, 1985) and ESWL (Alken *et al.*, 1984).

Initially, only small calculi were treated by PCN and extraction. The ability to remove over 80% of renal stones by PCNL was achieved by the addition of ultrasonic and electrohydraulic lithotripsy and the technique of multiple nephrostomy punctures into separate calices (Smith and Lee, 1983). The cautious introduction of ESWL for small, uncomplicated stones (Chaussy and Schmeidt, 1983) was extended over 2 years to treat up to 70% of all stones (Eisenberger *et al.*, 1985). Large staghorn calculi, however, require multiple time-consuming operating sessions, anaesthetics and nephrostomy tracks (Smith and Lee, 1983) with PCNL. These need to be coupled to repeated and complicated treatment sessions by ESWL, often with a high incidence of obstruction caused by sand masses (Eisenberger *et al.*, 1985).

ESWL and PCNL are suitable for patients of any age. Both techniques may be performed after previous open renal surgery or repeated after PCNL or ESWL. Local anaesthesia may sometimes be used for simple percutaneous extractions but complex percutaneous procedures and/or ESWL treatments require regional or general anaesthesia. PCNL may be performed on a conventional operating table, although preferably

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under image intensifier control. Access requires a nephrocutaneous puncture and track dilatation. Stones are located, fragmented and extracted directly under vision. The patient remains in a fixed prone position during the procedure. The larger stones are fragmented using unfocused shockwaves from an electrohydraulic probe or by the direct drilling effect produced by ultrasonic vibrations along a hollow metal probe. Electrohydraulic lithotripsy breaks stones into multiple fragments of less than 1 cm in size that can be easily grasped and removed with forceps. Ultrasonic lithotripsy creates smaller particles of 2 to 3 mm which are aspirated along the lumen of the ultrasonic lithotrite. Following successful PCNL by either method, the entire stone mass is removed from the kidney through the nephrostomy track at the time of surgery.

Conversely, using ESWL, the treatment suite is purpose-built and comprises a combination of a hydraulic frame to suspend the patient in a water bath and computerised radiological equipment. Calculi are localised entirely by radiological techniques. This involves biplanar fluoroscopy and image intensification and requires the patient and therefore the calculus to be moved hydraulically on the supportive frame for accurate localisation during treatment. The shockwaves are generated outside the body and are precisely focused on to the calculus. The stone is fragmented to sand-like particles with an average diameter of 2 mm or less (Drach and Chaussy, 1984) which are passed spontaneously in the urine over the following days or weeks. Immediately after the end of treatment by ESWL, most or all of the particles still remain within the kidney. The average operative treatment time for ESWL is 23.5 min, which is approximately half of the operative time for PCNL (Wickham *et al.*, 1985). Radiation exposure to the patients and surgeon from PCNL procedures (19.5 rads) is considerably higher than for ESWL (8.9 rads), to which only the patient is exposed (Fuchs *et al.*, 1984). Intra-operative complications during ESWL are few: hypotension or cardiac arrhythmias can occur. Post-operatively, obstruction from sand masses in the ureter or kidney requires endourological intervention in approximately 20% of cases (Alken *et al.*, 1985). These may be anticipated by close ultrasonic and radiological monitoring to prevent serious complications. Following ESWL, stone fragments remaining in the kidney that require further treatment by ESWL after at least 3 months occur in only 3% of cases (Eisenberger *et al.*, 1985).

During PCNL, significant operative complications including failed track, lost track, haemorrhage, trauma to the collecting system, "TUR syndrome", septicaemia and incomplete stone removal may occur. In the post-operative period, secondary haemorrhage that may even require segmental embolisation and septicaemia are the most serious complications, as well as persisting urinary fistula, ileus or pain (Segura, 1984). Following PCNL, an incidence of 9% of residual stone fragments has been reported (Payne *et al.*, 1985). An average in-patient stay of 3 to 4 days can be expected for treatment by either ESWL or PCNL (Smith and Lee, 1983; Wickham *et al.*, 1985). Following ESWL, over half of the patients do not require analgesia and less than a third require parenteral analgesia (Wickham *et al.*, 1985). Conversely, following PCNL, over half of the patients require parenteral analgesia and only 9% require no analgesia at all (Fair, 1986).

The major limitations to the treatment of renal calculi by ESWL are the size of the stone and obstruction distally. The anatomy of the stone within the kidney is not relevant, provided that it can be radiologically located by the image intensifier. Conversely, site is of prime importance for treatment by PCNL. Peripheral and multiple stones may require many separate nephrostomy punctures and repeated anaesthetics to gain access to all of the stones. As the stones are removed through a nephrocutaneous track, the problems of stone bulk, distal obstruction to urinary drainage and subsequent ureteric obstruction by stone fragments do not generally complicate percutaneous procedures.

Combinations

Most stones unsuitable for ESWL (15%) may be treated by PCNL and/or ureterorenoscopy (URS) and only a minority require open surgery (Alken *et al.*, 1985). Extracorporeal fragmentation of large calculi (>3 cm) may result in a high incidence of ureteric and renal obstruction and subsequent pain, hydronephrosis, urosepsis and renal failure (Eisenberger *et al.*, 1985). These complications may be avoided by PCNL prior to ESWL treatment. This reduces the stone mass and provides a nephrostomy conduit forming a large alternative pathway for the stone fragments that follow ESWL and also avoids obstructive complications. Using this combined technique, even complete staghorn stones may be treated without open surgery. Stones in solitary kidneys are difficult problems no matter what method of treatment is employed. A fine PCN or debulking PCNL prevents obstructive renal failure following treatment by ESWL. Patients presenting with acute obstructive sepsis or renal failure can be acutely relieved by simple PCN drainage under local anaesthesia and antibiotic therapy as appropriate. Once stabilised, conventional management by ESWL or PCNL can be performed as safe elective non-emergency procedures.

Following ESWL for any stone, there is always the possibility of ureteric obstruction (Eisenberger *et al.*, 1985). Percutaneous facilities must be available to manage these complications (Wickham *et al.*, 1985). Large residual stone fragments following ESWL may be treated again by ESWL or extracted by PCNL. These fragments may be extremely dense and hard, especially those derived from cystine stones, and can be managed by using a combination of ESWL fragmentation and chemolytic dissolution through a PCN after fragmentation (Schmeller and Chaussy, 1984).

By considering the limitations and advantages of ESWL, PCNL and open surgery, we have established a plan for the management of upper urinary tract calculi (Table).

Calculi less than 3 cm in diameter seldom cause obstructive complications provided that the distal urinary tract is not obstructed. If above the iliac crest or in the kidney, they can be localised radiologically for ESWL provided that the patient is not obese or there is no anatomical deformity, such as a severe scoliosis. We prefer to manipulate the ureteric stones back into the kidney as fragmentation is more effective within the pelvis. If this is not possible, they are treated *in situ* in the ureter with a ureteric catheter alongside to provide a capillary fluid slit next to the stone (Alken *et al.*, 1985). Over 90% of calculi can be primarily treated by ESWL (Webb *et al.*, 1985). Stones which are too large, impacted in the ureteric wall or too hard or dense, such as large cystine calculi, do not fragment satisfactorily with ESWL. Obstructive complications inevitably follow if these stones are treated in this manner. Any obstruction distal to the stone will inhibit the passage of stone particles, even after satisfactory fragmentation. Stones that cannot be placed within the shockwave focus cannot be treated by ESWL.

PCNL does not require radiological focusing and removes stones through a nephrostomy. This enables the extraction of a further 6% of renal and ureteric calculi without the need for open surgery (Webb *et al.*, 1985). Only irreversible bleeding disorders remain a contraindication.

Complicated calculi may be treated by combining the advantages of PCNL and ESWL. In solitary kidneys and following fragmentation of large stones by ESWL, obstructive complications can be avoided by an initial PCN to decompress the urinary system and PCNL to reduce the bulk of stone for subsequent fragmentation. Percutaneous punctures provide limited access to complex peripheral caliceal stones. These are easily imaged and treated by ESWL and the systematic combination of these two techniques enables these and other residual stones following ESWL or PCNL to be treated.

Obstructive complications either follow ESWL or present *de novo*. Even patients who are extremely ill can be relieved by simple PCN under local anaesthesia and converted to a stable clinical condition for elective treatment. The existing PCN may then be used for PCNL if appropriate. We have observed that ureteric fragments that persist following ESWL often pass rapidly after the insertion of a PCN.

Percutaneous incision of pelviureteric junction strictures (Wickham and Kellett, 1983) is an effective alternative to pyeloplasty in selected cases. Where a stone coexists, it is appropriate to remove it at the same operation.

What then are the indications for open surgery in the remaining patients? Kidneys requiring removal for non-function or sepsis in the presence of stone are managed by a simple nephrectomy. Anatomical corrections such as pyeloplasty, ureteric reimplantation or stricture corrections require open repair. Large impacted ureteric stones that are above the iliac crest and cannot be manipulated to the kidney and those below the iliac crest which cannot be managed by endoscopic ureterolithotripsy may be simply removed by open ureterolithotomy.

Selection of the most appropriate therapy is more complicated for the large renal calculus. Stones whose major bulk is intrapelvic, with few caliceal extensions, wide infundibula and caliceal necks, would conventionally be removed by the Gil-Vernet extended renal sinus approach and the removal of the majority of their mass can be achieved by a single PCNL. This procedure leaves only peripheral stone fragments in freely draining calices in the presence of a large nephrostomy conduit. The remaining stone is easily fragmented by ESWL and passes through the nephrostomy. Complex stones that are predominantly peripheral in the kidney anatomically, have multiple caliceal extensions and are associated with narrow infundibula and a small intrarenal pelvis are unsuitable for either significant debulking or drainage from

Table Management of Renal and Ureteric Calculi

ESWL		PCN and PCNL					Open surgery
Indications	*Contraindications*	*Indications*				*Contraindications*	*Indications*
		Alternative to ESWL	*Combined with ESWL*	*Emergency procedures*	*Synchronous percutaneous procedures*		
Stone < 3 cm diameter Radiological localisation possible Adequate drainage distal to stone	Large stone (> 3 cm) Cannot focus radiologically (*a*) Obesity (> 135 kg) (*b*) Height (< 130 cm, > 200 cm) (*c*) Anatomical (*eg*, scoliosis) (*d*) Lucent stone (large) Dense, hard stone (*eg*, cystine) Impacted ureteric stone Coagulation defect	Cannot focus for ESWL Obstruction distal to stone Dense, hard stone Existing percutaneous nephrostomy Impacted upper ureteric stone ESWL unavailable	Stone mass > 3 cm Staghorn calculus Solitary kidney Residual stone Obstruction following ESWL	Obstructive urosepsis Obstructive renal failure Hydronephrosis	Pyelolysis Others	Coagulation defect	Staghorn calculus Extremely large dense stone Pyeloplasty and pyelolithotomy Other anatomical corrections Nephrectomy for non-function or sepsis Impacted, large ureteric calculi Correction of ureteric anatomical abnormalities

PCNL without undertaking multiple punctures and anaesthetics. The associated poorly draining calices are also unsuitable for fragment passage following ESWL. Fortunately, these kidneys are usually suitable for a one-stage clearance by open nephrolitotomy and multiple radial nephrotomies, and in our experience are best treated in this way.

Thirdly, extremely large, long-standing, dense calculi within a dilated kidney with a thinned renal cortex require long and multiple percutaneous procedures to debulk them; they do not fragment well using ESWL and are best removed by a single open nephrolithotomy.

To select the most suitable stones for open surgery now requires experience in the alternative techniques. Most calculi may be safely removed by ESWL, PCNL or by a combination of the two.

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The Authors

D. R. Webb, DRCOG, FRACS, Urologist, Devonshire Hospital Lithotripter Centre; Honorary Senior Lecturer, Institute of Urology.

S. R. Payne, FRCS, Fellow in Percutaneous Renal Surgery, Institute of Urology.

J. E. A. Wickham, MS, FRCS, Director, Academic Unit, Institute of Urology and Devonshire Hospital Lithotripter Centre.

Requests for reprints to: D. R. Webb, 27 Welbeck Street, London W1M 7PG.

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Pyeloureterostomy or Ureteroneocystostomy in Renal Transplantation?

R. LANDAU, J. R. BOTHA and J. A. MYBURGH

Department of Surgery, University of Witwatersrand Medical School and the Johannesburg Hospital, Johannesburg, South Africa

Summary—A retrospective comparison of pyeloureterostomy and external ureteroneocystostomy as methods of reconstructing the urinary tract in 128 renal transplants is presented. There was one urological complication in 52 pyeloureterostomies (1.9%) compared with 4 in the 76 ureteroneocystostomies (5.3%). 6/0 Polydioxanone (PDS) is preferred to Prolene for the anastomosis because of possible calculus formation on the latter.

Wound sepsis is commoner in pyeloureterostomies undergoing concomitant nephrectomy, despite prophylactic antibiotics, though this is not statistically significant and the overall sepsis rate is higher for ureteroneocystostomy. Nephrectomy was avoided in 17 selected cases by simply ligating the recipient ureter where the pre-transplant urine output was low. Two of these patients developed hydronephrosis in the isolated kidney and required later nephrectomy.

In 1936 the Russian surgeon, Voronoy, attempted the first (albeit unsuccessful) renal transplant (Stickel and Seigler, 1981). However, because of the problems of tissue rejection it was not until 1959 that Murray in Boston and Hamburger in Paris were able to perform the first successful allograft. Now, 25 years later, although the technique of revascularisation has become standard, reconstruction of the urinary tract continues to have a significant complication rate.

Anastomosis of the donor ureter to recipient bladder (ureteroneocystostomy), employing either an internal or external approach, is the method favoured by nearly all transplant surgeons. However, this is complicated by ureteric obstruction or fistula formation in 7 to 8% of grafts (Tables 1 and 2).

A second method of urinary tract reconstruction, pyeloureterostomy, was used by early transplant surgeons, but fell from favour because of a prohibitive urinary leak rate ranging from 8 to 26% in various series (Greenberg *et al.*, 1977). Here the donor pelvis is sutured end-to-end to the recipient ureter. Despite its theoretical advantages this technique was subsequently used only when the donor ureter was short or damaged or the pelviureteric junction was abnormal.

In 1982 Jaffers *et al.* reported a series of 260 pyeloureterostomies with a complication rate of only 3% in the final period of the study. This raises the question as to which is the preferred technique of urinary tract reconstruction in renal transplants. A retrospective analysis of the Johannesburg Hospital experience with these two methods is presented.

Patients and Methods

From March 1983 to January 1985, 128 consecutive renal transplants were performed on 119 patients at the Johannesburg Hospital, 115 from cadaver donors. External ureteroneocystostomy was used in 76 patients and pyeloureterostomy in 52, the choice depending on the surgeon's personal preference, and the presence or absence of a previous nephrectomy or a previous transplant. The latter may make it technically difficult or even impossible to use the recipient's ureter.

Prophylactic antibiotics were not used routinely

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Table 1 Urological Complications of Internal Ureteroneocystostomy

	Reference	*No. of Pts*	*No. of complications*	*Percentage of complications*
1973	Malek *et al.*	93	7	5.0
1974	Bewick *et al.*	196	27	
1974	Salvatierra *et al.*	470	3	
1975	Donohue *et al.*	88	4	
1975	Holden *et al.*	141	19	
1975	Leary *et al.*	79	1	
1977	Greenberg *et al.*	47	6	
1979	McDonald *et al.* (review of 22 centres)	2091	189	9.0
1981	Mundy *et al.*	968	131	13.6
1983	Sagalowski *et al.*	505	16	3.1
	Total	4678	393	8.4

Table 2 Urological Complications of External Ureteroneocystostomy

	Reference	*No. of Pts*	*No. of complications*	*Percentage of complications*
1969	Woodruff *et al.*	33	1	3.0
1971	Robson and Calne	147	17	11.5
1975	Konnak *et al.*	170	12	7.0
1976	Eikhoff *et al.*	298	13	3.4
1979	McDonald *et al.*	88	0	0
1979	Meech *et al.*	266	40	15.1
1981	Wasnick *et al.*	183	8	4.0
1982	Van Cangh *et al.*	874	26	3.0
1982	Waltke *et al.*	72	8	11.0
1983	Myburgh *et al.*	525	47	9.0
	Total	2656	172	7.0

but all patients undergoing concomitant nephrectomy received a single intravenous dose of cloxacillin and tobramycin pre-operatively. The anastomosis in both groups was performed using 7/0 Prolene for the first 28 patients, and thereafter 6/0 Polydioxanone (PDS), employing continuous sutures in an oblique anastomosis. Stents were not inserted. Drains, where used, were of the closed suction type and were removed 24 h post-operatively. The urinary catheter was removed after 48 h, irrespective of the type of anastomosis.

Patients undergoing a pyeloureterostomy had an ipsilateral nephrectomy. This was performed extraperitoneally by extending the inguinal incision. However, where the kidney was atrophic and urine output less than 500 ml per day, the ureter was simply ligated and divided without performing a nephrectomy (17 cases). In five patients, nephrectomy had been performed at some time before the transplant.

The donor pelvis was intrarenal in 9 of the 52 pyeloureterostomies. In these a high oblique ureteroureteric anastomosis was performed. These cases are included as pyeloureterostomies in this study.

Results

Five ureteric complications occurred in the 128 transplants, 4 in the ureteroneocystomy group (5.3%) (Table 3). The two groups were well matched as regards numbers of related living donors, where donor hilar dissection is more extensive, and the incidence of diabetes which has also been implicated as a risk factor in ureteric fistulas (Sagalowski *et al.*, 1983). None of the five complications was secondary to wound sepsis.

Of the ureteroneocystostomies, one dehisced and the patient developed a urine leak in the immediate post-operative period. Despite three attempts to re-anastomose the ureter, wound sepsis followed and the graft was eventually removed. Two patients developed ureteric obstruction, one from distal ureteric necrosis and one from oedema with superimposed blood clot obstruction. Both grafts were saved by resection and re-anastomosis, and

Table 3 Details of Complications

A: Local complications in 128 renal transplants

	Ureteroneocystostomy (76)	*Pyeloureterostomy (52)*
Wound haematoma	1	3
Urine leak/obstruction	4 (5.3%)	1 (1.9%)
Wound sepsis—primary	4 (5.3%)	4 (7.7%)
Total	7 (9.3%)	4 (7.7%)
Hydronephrosis of recipient kidney	0	2

B: Factors affecting complication rate

	Ureteroneocystostomy (76)	*Pyeloureterostomy (52)*
Related living donors	7	5
Diabetes	9	5
Nephrectomy	2	30
Drains	62 (81%)	36 (69%)

sepsis did not occur. The fourth ureteroneocystostomy was re-explored for an early urine leak and a small hole found in the bladder close to the anastomosis. This was sutured and no further problems arose.

The single pyeloureterostomy re-explored for a urine leak had a sharp angulation obstructing the renal pelvis proximal to the anastomosis, which was intact, and a perforation in the pelvis above that. The recipient ureter was slightly strictured at the vesicoureteric junction. It is postulated that pelvic obstruction caused pressure necrosis, possibly in conjunction with injury to the pelviureteric artery causing ischaemia. The kidney was saved by re-anastomosis over a stent, and though a urinary fistula persists, it appears to be closing.

Primary wound sepsis rates in the two types of anastomosis are similar (5.3 and 7.7%). However, three patients with ureteroneocystostomies in whom reopening of their wound was necessary for a urine leak in two cases, and haematoma in the other, developed secondary wound sepsis. Two of the ureteroneocystostomies had comcomitant nephrectomies for uncontrolled hypertension. One developed wound sepsis.

Ureteric ligation without concomitant nephrectomy was performed in 17 pyeloureterostomies. Complications ensued in two of these patients. In both instances the procedure should not have been performed as the patients were passing far more than 500 ml of urine per day. As expected, the obstructed kidneys developed hydronephrosis and nephrectomy was required later.

Though wound sepsis is somewhat more frequent after ureteroneocystostomy, the nephrectomy usually required for a pyeloureterostomy appears to be associated with a higher infection rate (Table 4) ($P<0.1$ >0.05). This difference cannot be attributed to other factors influencing wound sepsis, namely diabetes, drain insertion, numbers of related living donors, haematoma formation and reopening of the wound, as they are more common in the group without nephrectomy.

Table 4 Incidence of Wound Sepsis

A: Wound sepsis in 52 pyeloureterostomies with or without nephrectomy

	Nephrectomy (30)	*No nephrectomy (22)*
	4 (13.3%)	0 (0%)

$x^2 = 3.18$ $P<0.1$ >0.05

B: Factors affecting wound sepsis

	Nephrectomy (30)	*No nephrectomy (22)*
Diabetes	1	4
Related living donors	3	2
Drains	20	16
Re-opened	2	2
Haematoma	1	2

In all four patients who developed wound sepsis after pyeloureterostomy, the nephrectomy was performed for purely technical reasons. The underlying renal diseases were polycystic kidneys, systemic lupus erythematosus, malignant hypertension and analgesic nephropathy. Only the last of these may have predisposed to infection.

Discussion

The commonest method of urinary reconstruction used to date is the transvesical (internal) ureteroneocystostomy described by Politano and Leadbetter in 1958. The bladder is opened and the ureter implanted through a small cystotomy and submucosal tunnel to prevent vesicoureteric reflux. Paquin described a modification of this technique in 1959, creating an internal ureteric nipple.

However, both cystotomies are prone to disruption and urinary fistula formation. Furthermore, the ureteric arterial supply is derived from a descending branch of the renal artery or its lower pole branch, which is easily damaged during harvesting of the kidneys. The length of ureter required for this technique, together with possible damage to donor periureteric tissues, increases the risk of ureteric ischaemia and necrosis. A review of 4678 transplants from 30 different centres (Table 1) shows an 8.4% urological complication rate. The mortality rate from these complications was reported to be 19.6% by McDonald *et al.* (1979) and 22% by Mundy *et al.* (1981).

An external ureteroneocystostomy was described by MacKinnon *et al.* in 1968 and Woodruff *et al.* in 1969. This was based on the 1896 technique of Witzel and a method of extravesical tunnelling reported by Lich *et al.* in 1961. The bladder is distended with fluid via a urethral catheter pre-operatively, allowing identification of its mucosa, which is sutured to the ureteric mucosa. The anastomosis is buried to form an extravesical tunnel. A separate cystotomy is thus not required and the length of donor ureter can be reduced.

A review of the literature with regard to the urological complications of this method is shown in Table 2. In 2656 transplants from 10 centres the complication rate was 7%, which differs little from that of the internal approach.

Before 1982 few centres recommended pyeloureterostomy as a primary technique for urinary reconstruction. The 3% complication rate reported by Jaffers *et al.* (1982) in their 260 transplants was attributed to meticulous surgical technique and the use of fine sutures. These authors felt that the high rate of fistula formation in previous series was due to chromic catgut sutures cutting through tissues. Initially Tevdek was used, but because of calculus formation on the sutures this was changed to 7/0 Prolene.

Despite the frequency of urinary fistulas in early studies of pyeloureterostomy (8-26%), the theoretical advantages of the procedure have been well described (Jaffers *et al.*, 1982). It avoids the problem of distal or total ureteric ischaemia which, if acute, may cause ureteric necrosis or oedema and obstruction. Chronic mild ischaemia may lead to fibrosis and eventual stricture formation at the vesicoureteric anastomosis.

Pelvic dissection is not required to expose the bladder. However, this is not a problem in the external type of ureteroneocystostomy. Pyeloureterostomy is useful when the donor ureter is short, particularly when anastomotic leaks have necessitated ureter resection prior to re-anastomosis. It avoids cystotomy with its accompanying problems of urine leaks, haematuria, clot retention and painful bladder spasms.

Provided the recipient's ureter is normal, vesicoureteric reflux should not occur. This has a reported incidence of 12 to 35% in ureteroneocystostomy (Debruyne *et al.*, 1978; McDonald *et al.*, 1979; Nghiem *et al.*, 1981) and apparently is not altered by an anti-reflux procedure. Several studies have shown no increased incidence of urinary infection in patients with reflux (Debruyne *et al.*, 1978; Nghiem *et al.*, 1981) and no renal damage if the urine remains sterile.

Lastly, because pyeloureterostomy preserves the normal ureteric orifice, retrograde catheterisation is still relatively simple at cystoscopy (Jaffers *et al.*, 1982). Such a procedure after a ureteroneocystostomy may well damage the anastomosis if performed in the early post-operative period.

The excellent results obtained with pyeloureterostomy at this centre tend to support the study of Jaffers *et al.* (1982). End-to-end suture of the full thickness muscular wall of the ureter and pelvis seems to be more satisfactory than suturing ureter to thin bladder mucosa. High ureteroureteric anastomosis in cases with intrarenal pelvices was performed fairly frequently without complication.

Monofilament absorbable PDS is now used in preference to Prolene at this centre. Prolene sutures have been noted to work through the wall of the ureter and intrude into its lumen, and calculi have been found on such sutures in animal studies at this university. Encrustations, and in one case a formed calculus, have been seen at cystoscopy in our unit.

The alleged disadvantages of pyeloureterostomy are that it requires meticulous technique and that a nephrectomy is necessary (Greenberg *et al.*, 1977; McDonald *et al.*, 1979; Jaffers *et al.*, 1982). The criticism that anastomotic complications may cause graft loss by excessively shortening the recipient ureter is disputed by Jaffers *et al.* (1982).

From this study it appears that a further disadvantage of pyeloureterostomy may be a higher wound sepsis rate when a nephrectomy is performed, though the numbers in this series are small and the overall sepsis rate is lower for pyeloureterostomy than ureteroneocystostomy (Table 4). Greater internal dissection and more forceful retraction causing excessive tissue trauma may be the factors responsible. Furthermore, nephrectomy prolongs the operation by as much as half an hour, which is a well known factor in promoting infection, particularly by *Staphylococcus pyogenes*. In this study 6 of the 11 cases of wound sepsis were staphylococcal, corresponding with the 68% incidence of staphylococci isolated from septic wounds reported in a previous study from this unit (Myburgh *et al.*, 1983). This showed a 15% sepsis rate with nephrectomy as opposed to 2% without. However, this high figure was related to the underlying renal disease necessitating nephrectomy, often analgesic nephropathy or chronic pyelonephritis. A nephrectomy for purely technical reasons would not be expected to cause infection.

Statistical analysis shows that the apparent relationship in this study is not significant. However, as the numbers involved grow, this may alter. Also, the sepsis rate is higher after nephrectomy despite the selective use of antibiotics in this group.

Few studies of wound sepsis in this situation are to be found in the literature, since most centres do not perform nephrectomy concomitantly with transplantation. In a series of 206 patients Turner *et al.* (1983) reported a 10.5% sepsis rate in 38 patients who had bilateral nephrectomies. This differs little from the non-nephrectomised group. Nevertheless, further studies may well confirm an association, indicating that concomitant nephrectomy is best avoided. Reports from several transplant centres show a reduction in wound sepsis rates from 10 to 25% without antibiotics to 1 to 2% with a single pre-operative dose regimen (Tilney *et al.*, 1978; Novick, 1981). However, 13.3% of our nephrectomised patients developed wound sepsis despite prophylactic antibiotics.

In this study nephrectomy was avoided in patients with low urine outputs by simply ligating the ureter, provided there was no urinary infection. Where urine output is greater than 500 ml per day it is considered safer to remove the kidney rather than risk subsequent hydronephrosis. End-to-side anastomosis of donor ureter to recipient ureter (McDonald *et al.*, 1979) may be a more satisfactory technique for avoiding nephrectomy, but urine reflux into the abnormal kidney constitutes a high risk of infection that may spread to the graft. However, an association between nephrectomy and wound sepsis is tenuous at present and the indication for such procedures as yet uncertain.

In conclusion, pyeloureterostomy has been used with great success at this centre. Should it supplant ureteroneocystostomy as the method of choice in reconstructing the urinary tract after transplantation? More experience with this promising technique at this and other centres is required to answer this question.

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The Authors

R. Landau, MB,BCh, Surgical Registrar.
J. R. Botha, MB,ChB, FCS(SA), Consultant Surgeon.
J. A. Myburgh, MB,ChM, FRCS, Professor, Head of Department of Surgery.

Requests for reprints to: R. Landau, Department of Surgery, University of Johannesburg Medical School, York Road, Parktown, Johannesburg 2193, South Africa.

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Renal Oncocytoma

H. J. E. LEWI, C. A. ALEXANDER and S. FLEMING

Departments of Urology, Radiology and Pathology, Western Infirmary, Glasgow

Summary—Oncocytic renal tumour is an uncommon tumour of the kidney, previously associated with a good outcome. Twenty-two patients are described in whom the incidence of metastatic disease was 18% and the overall 5-year survival rate 65%.

Renal oncocytoma is an infrequently reported tumour of the renal parenchyma. It is composed of oncocytes, which are uniform well differentiated granular esoinophilic cells arranged in a tubular, alveolar or papillary pattern. The light microscopic appearances are due to large numbers of mitochondria in the cytoplasm of the epithelial tumour cells, which are thought to be derived from the epithelium of the proximal convoluted tubule (Klein and Valensi, 1976), although Fleming *et al.* (1985) have questioned this. Klein and Valensi (1976) reported 13 such tumours and suggested that they were a distinct pathological entity, with a favourable prognosis when compared with other forms of renal carcinoma. Subsequent series have largely confirmed this: of 141 patients previously reported, only four (2.8%) have died of metastatic carcinoma (Lieber *et al.*, 1981; Fairchild *et al.*, 1983).

Twenty-two patients with renal oncocytoma are described, four of whom have developed metastatic disease.

Patients

Between 1965 and May 1984, 233 nephrectomies were performed for renal tumour in the Western Infirmary, Glasgow: 16 of these (7%) were found to be oncocytic renal tumours. A further six patients were referred for histological evaluation and study, making a total of 22 cases.

There were 11 males and 11 females aged between 26 and 86 years (mean ± 15.4 years). Thirteen tumours were right-sided and 9 were left-sided. There were no bilateral tumours.

Clinical Presentation

In nine patients (41%) the renal tumours were asymptomatic and were discovered incidentally during routine investigation for hypertension (2), during routine post-operative follow-up for other conditions (3) and during investigation of frequency (1) and haemospermia (1). One patient was discovered incidentally to have an oncocytoma following bilateral nephrectomy for chronic renal failure and hypertension prior to renal transplantation, and one renal tumour was found at *post mortem* following death from bronchopneumonia.

Seven symptomatic patients presented with haematuria and five with loin pain. The last patient presented with a pathological fracture of the left femur due to metastatic renal tumour.

Radiological Investigations

Intravenous urography (IVU) was diagnostic of a space-occupying lesion or renal tumour in 18 of 21 cases; ultrasonography (USG) was performed in 11 cases and was confirmatory in nine; selective renal angiography was diagnostic in seven cases. In one patient investigated for haematuria, and whose tumour had not been diagnosed by IVU, the IVU remained consistently negative. The diagnosis was finally made on repeat cystoscopy, when blood was seen issuing from the right ureter, and a right ascending pyelogram demonstrated a filling defect in the right renal pelvis. Another patient was undergoing routine follow-up after proctocolec-

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tomy for long-standing ulcerative colitis, when a left loin mass was noted. Both IVU and USG demonstrated an apparently cystic mass but angiography demonstrated a tumour circulation to the lower pole in the left kidney. In the third and final case, the patient presented with renal failure and hypertension, and initially was treated by haemodialysis. Both kidneys were non-functioning on IVU and USG showed them to be small, shrunken and scarred. Bilateral nephrectomy was performed prior to transplantation and an incidental oncocytoma of the right kidney was found.

Radiological Appearances

No distinctive features were noted on IVU and USG, the appearances being those of large, solid, space-occupying lesions. In the seven patients in whom angiography was performed there were five cortical and two central lesions. Selective angiography demonstrated the classical "spoke-wheel" pattern of Weiner and Bernstein (1977) in only one of the five cortical lesions (Fig. 1) and all of these tumours demonstrated a well circumscribed margin surrounding a central dense parenchymal area with a central vascular blush (Fig. 2). There was no arteriovenous shunting or contrast pooling. The two central lesions were less well defined and demonstrated tumour hypervascularity with contrast pooling.

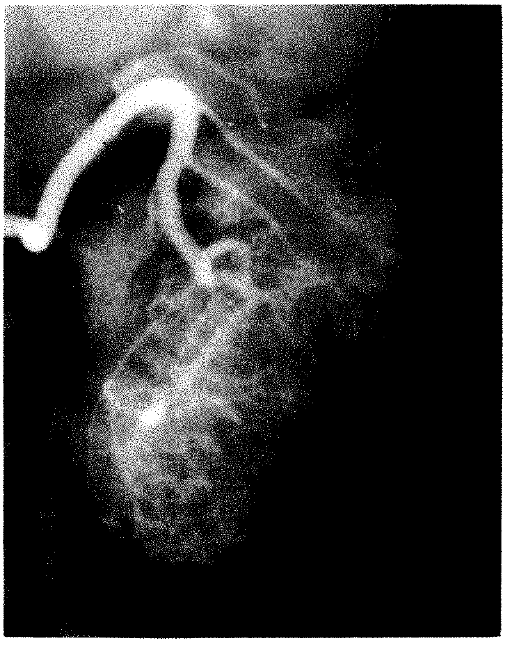

Fig. 1 Angiogram of left renal oncocytoma demonstrating the "spoke-wheel" pattern of the tumour circulation.

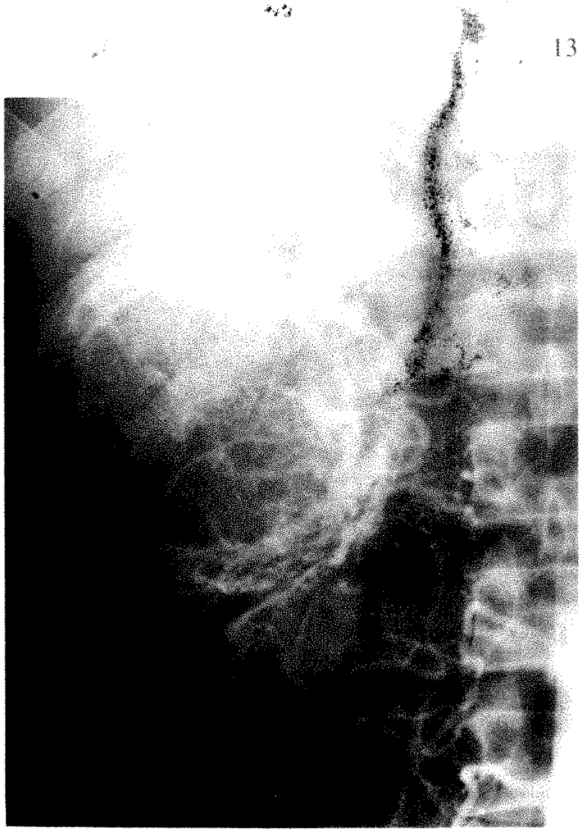

Fig. 2 Angiogram of right renal oncocytoma demonstrating a well circumscribed margin surrounding a central dense core.

Pathological Assessment

Histological slides and paraffin-embedded tissue blocks were available for review from all 22 patients. Material for ultrastructural examination was available in three cases. The original gross descriptions and histological slides were reviewed by one pathologist (SF). The diagnosis was confirmed in all cases.

The neoplasms were graded according to the criteria of Lieber *et al.* (1981). Grade 1 tumours (Fig. 3A) consisted entirely of uniform well differentiated tumour cells with abundant granular eosinophilic cytoplasm and small dense circular nuclei, showing minimal pleomorphism. Mitotic figures were not present and necrosis was not a feature. Grade 2 tumours (Fig. 3B) showed more variation in cell size, nuclear pleomorphism and overall morphology, although mitosis and necrosis were not seen. Fifteen cases of more pleomorphic tumours (grades 3 and 4) with mitotic figures, necrosis, marked variation in cell morphology or containing areas of clear cell carcinoma, had been previously excluded from the study.

The electron micrographs from three patients

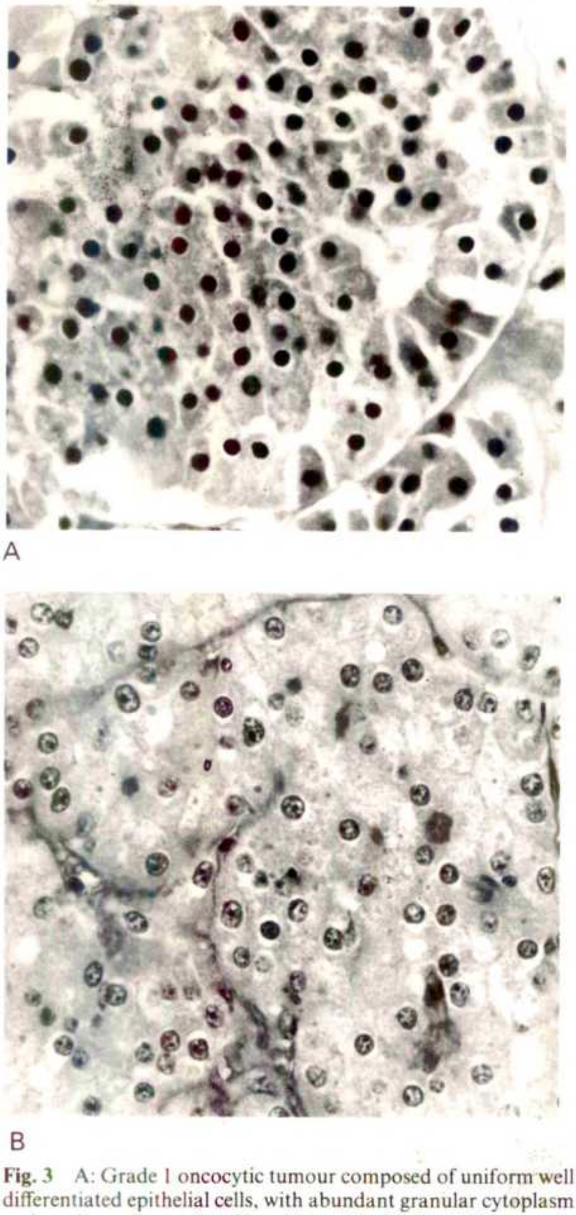

Fig. 3 A: Grade 1 oncocytic tumour composed of uniform well differentiated epithelial cells, with abundant granular cytoplasm and small regular nuclei. (H and E × 166). B: Grade 2 oncocytic tumour. The overall morphology is similar to that seen in the Grade 1 tumour, but cellular and nuclear pleomorphism is apparent. (H and E × 166).

were reviewed. The tumour cells were found to have numerous mitochondria within the cytoplasm and in many tumour cells microvilli were noted on the apical cell membrane. Strands of rough endoplasmic reticulum were present in a few tumour cells. The histological slides from the metastasis of one patient were available for study. The sections consisted of a bronchial biopsy and a partial colectomy specimen; both demonstrated metastatic oncocytic renal tumour and showed a higher degree of pleomorphism than the Grade 2 primary. Mitotic figures and necrosis with an inflammatory infiltrate were present in both specimens.

Results

At operation, 15 tumours were Stage I, three were Stage II, three Stage III, and the final patient, who presented with a metastatic deposit in the left femur, was Stage IV. Using the previously documented histological criteria, 11 patients had grade 1 and 11 had grade 2 tumours.

In one case, an asymptomatic grade 1 oncocytoma was found at *post mortem*. In the 21 patients who underwent nephrectomy for renal oncocytoma, two have been lost to follow-up and two have been followed up for less than 1 year. Three patients died in the early post-operative period, two within the first 30 days following nephrectomy; one of them had presented with a metastatic deposit in the left femur and the renal tumour was a grade 1 oncocytoma. The third patient died from an intracerebral haemorrhage 30 days after renal transplantation, some 2 months after bilateral nephrectomy. Of the remaining 14 patients, five have since died; three had no evidence of disease 2 to 11 years following nephrectomy and two did have evidence of metastatic disease. One of the latter patients developed a confusional state 3 months after nephrectomy; the renal tumour was a grade 1 oncocytoma. Brain scan revealed a metastatic deposit in the frontal lobes and the patient died 12 months post-operatively. The second patient (with a grade 2 renal oncocytoma) died from extensive intra-abdominal recurrence 6 years following nephrectomy. One of the nine surviving patients, with a grade 2 oncocytoma, has a biopsy-proven lung metastasis (treated by local radiotherapy) that developed 14 years after nephrectomy. This patient subsequently developed large bowel obstruction for which a colectomy was performed; examination of the resected specimen demonstrated metastatic oncocytic tumour. A further eight patients are alive, with no evidence of disease 18 months to 8 years following operation.

As already noted, four patients developed metastases from their renal oncocytoma, two with grade 1 and two with grade 2 tumours. The overall 1-year, 5-year and 10-year cumulative survival rates for patients with oncocytic renal tumours were 86, 65 and 37% respectively.

Discussion

Oncocytoma is a recognised, though infrequent renal tumour, and previous studies have shown that it accounts for 3 to 6% of all renal tumours (Ambos *et al.*, 1978; Fairchild *et al.*, 1983). The diagnosis is based solely on histological appearances and it has been reported that the biological behaviour of the tumour is related to the degree of cellular and nuclear pleomorphism present (Lieber *et al.*, 1981). Although the division into grade 1 and grade 2 renal oncocytoma is arbitrary, Lieber *et al.* (1981) and Fairchild *et al.* (1983) have clearly demonstrated that grade 1 oncocytoma has a low malignant potential. In the 113 cases reviewed by Fairchild *et al.* (1983), metastases did not occur and it was concluded that grade 1 renal oncocytoma was a "pre-malignant lesion". Grade 2 renal oncocytoma appears to be less common but more aggressive than the grade 1 lesion, and it behaves in a similar way to renal carcinoma. Lieber *et al.* (1981) reported 28 cases of grade 2 oncocytoma, representing 30% of their documented cases. In this group, metastases occurred in four patients (14%) and lymph node involvement was noted in a further two (7%); they concluded that dedifferentiation of the tumour was directly related to its ability to spread beyond the kidney.

Tissue sampling is a problem in a retrospective study such as this, where histological assessment is of fundamental importance. Many of the cases antedate the first series of renal oncocytoma reported by Klein and Valensi (1976) and although adequate sampling for diagnosis has been made, it is clearly impossible to exclude the possibility that either clear cell areas, or areas of pleomorphic (grade 3 or 4) tumour, are present within an unsampled area of the specimen. This difficulty has been previously discussed by Lieber *et al.* (1981) and accepted as an inevitable problem of retrospective histological studies.

In the present series, the incidence of renal oncocytoma amongst renal carcinoma was 7%, and our findings differed from those of other series in two respects. Firstly, half of the 22 patients had grade 2 oncocytic tumours. Secondly, four patients (17%) developed metastases and three subsequently died. Two of these patients with metastatic disease presented with a grade 1 and two with a grade 2 renal oncocytoma, indicating that both histological subtypes have the propensity to metastasise.

In previous reports of renal oncocytoma, much has been made of the angiographic features of the tumour, such as its "spoke-wheel" appearance (Weiner and Bernstein, 1977; Ambos *et al.*, 1978) or the presence of a well circumscribed margin surrounding a central dense area (Sos *et al.*, 1976; Ambos *et al.*, 1978; Bonavita *et al.*, 1981). It should be noted that similar appearances may occur in up to 15% of renal carcinomas (Ambos *et al.*, 1978) and it would be unwise to make a pre-operative diagnosis based upon the angiographic features.

Our findings indicate that renal oncocytoma is not a benign or pre-malignant tumour, and also that the ability of the tumour to metastasise appears to be unrelated to the histological appearances. The presence of a renal oncocytoma should not alter the post-operative management of a patient with a renal tumour, since metastases may develop as late as 14 years following nephrectomy. There appears to be no place for partial nephrectomy, as previously advocated by Weiner and Bernstein (1977), Ambos *et al.* (1978) and Lieber *et al.* (1981), except in the presence of bilateral tumours or where the tumour occurs in a solitary kidney.

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The Authors

H. J. E. Lewi, FRCSE, Senior Registrar in Urology.

C. A. Alexander, DMRD, FRCR, formerly Senior Registrar in Radiology. Now Consultant Radiologist, Royal Alexandra Infirmary, Paisley.

S. Fleming, BSc, MB, BCh, formerly Registrar in Pathology. Now Lecturer in Pathology, University of Southampton.

Requests for reprints to: H. J. E. Lewi, Department of Urology, Western Infirmary, Glasgow G11 6NY.

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Urinary Tract Lymphoma

H. J. E. LEWI, J. D. STEWART, M. SEYWRIGHT, S. FLEMING, R. F. DEANE and K. F. KYLE

Departments of Urology and Pathology, Western Infirmary, Glasgow

Summary—Urinary tract involvement by non-Hodgkin's lymphoma is uncommon and whilst extranodal disease may be the first manifestation of NHL in 15% of patients, the primary site of origin of NHL in the urinary tract is very rare. At the time of diagnosis, apparently primary urogenital lymphoma is often widely disseminated, with a correspondingly poor prognosis.

Involvement of the urinary tract by non-Hodgkin's lymphoma (NHL) is uncommon. This occurs in less than 10% of patients with the disease and manifests itself as a primary urological problem in less than 1% (Watson *et al.*, 1949; Weimar *et al.*, 1981). In rare instances the primary site of origin of HNL may appear to be within the urinary tract, but at presentation the tumour is often widespread and chemotherapy may be the only form of treatment available (Whitmore *et al.*, 1982).

Three patients with widespread disease are presented, in each of whom the primary site of NHL appeared to be within the urinary tract.

Case 1 (GN)

A 64-year-old man presented with frank painless haematuria. Intravenous urography demonstrated obstructive uropathy and at cystoscopy an unremarkable large infiltrating bladder tumour was noted. The tumour was resected and histology demonstrated an infiltrating atypical tumour of the bladder, consisting of sheets of large round cells consistent with, but not diagnostic of, a diffuse large cell NHL (Fig. 1). Further investigation revealed enlarged para-aortic nodes and the patient was initially treated by radiotherapy. Over a 2-month period, pulmonary "lymphangitis carcinomatosis" developed and chemotherapy with cisplatin was commenced. After 5 cycles, methotrexate and chlorambucil were added to the regime, but after 3 pulses of the combined regime the patient had a haematemesis. Endoscopy revealed multiple gastric erosions with ulceration of the duodenum; histological examination of a gastric biopsy demonstrated pathology identical to that of the resected bladder tumour. Immunocytochemistry demonstrated antibody staining to common leukocyte antigen, confirming the lymphocytic origin of these cells, and identified both the bladder and gastric tumours as diffuse large cell NHL. The patient was commenced on a combination of cyclophosphamide, vincristine, Adriamycin and prednisolone, but after 5 pulses he became comatose and subsequently died 18 months after presentation. At post mortem there was evidence of widespread disease, with metastases in the lungs and brain.

Case 2 (GD)

A 63-year-old man presented with acute retention, pyrexia and perineal pain. Examination revealed a grossly enlarged swollen prostate and he was initially treated by catheter drainage and antibiotics, but subsequently underwent prostatectomy under antibiotic cover. Histology of the specimen demonstrated dense infiltration of the prostate by large lymphocytic cells consistent with the findings of a diffuse large cell NHL (Fig. 2). Postoperative investigations demonstrated numerous focal defects in the lungs and an enlarging mass in the right maxillary antrum. Biopsy of the antral mass demonstrated histology identical to that seen in the prostate. In view of the stage IV nature of the disease the patient was referred for chemotherapy and had an initial good response to a combination of cyclophosphamide, Adriamycin, bleomycin and VP 16, with resolution of the lung deposits. After 3 cycles of chemotherapy he developed bronchopneumonia and subsequently died. Post mortem demonstrated no evidence of residual disease.

Case 3 (WS)

A 29-year-old man presented with progressive dyspnoea and chest X-ray demonstrated enlargement of the hilar lymph nodes; he was commenced on mustine and dexamethasone, with good response. Subsequent investi-

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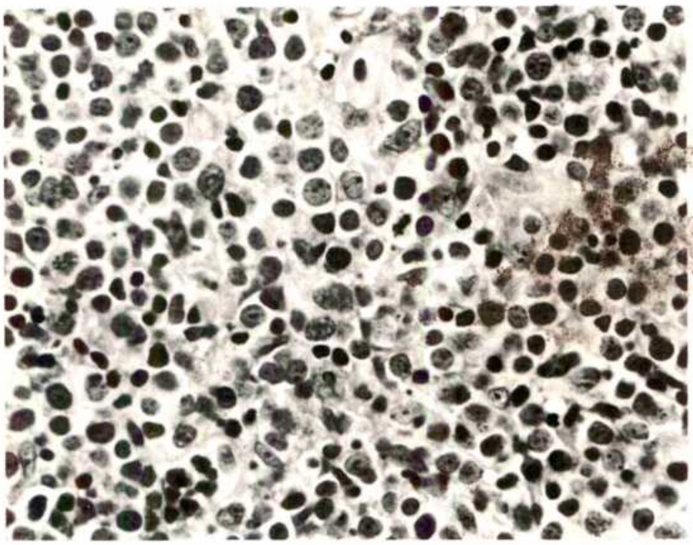

Fig. 1 Infiltration of the bladder by large pleomorphic round cells (diffuse large cell NHL). (H and E × 360).

gations revealed a grossly enlarged non-functioning right kidney with features consistent with those of a renal tumour. At laparotomy there was no evidence of tumour spread or retroperitoneal disease and radical nephrectomy was performed. Histology revealed that the kidney was completely replaced by a localised NHL of the large cell centroblastic variety (Fig. 3). The patient was given 6 cycles of chlorambucil (10 mg daily), procarbazine (100 mg daily) and prednisolone (50 mg daily) given orally on days 1 to 14, and vinblastine (5 mg) given intravenously on days 1 and 7 of the cycle, and then put on maintenance chlorambucil (10 mg daily) and prednisolone (10 mg daily). He remained well for 18 months but then developed a right inguinal node mass, treated by excision and local radiotherapy. The excised mass had histological features identical to those of the right kidney. Eight months later a further mass appeared in the left inguinal region and again was treated by local radiotherapy and excision. The patient remained well for a further 2 years but then developed a right axillary node mass, treated by local excision and radiotherapy, with the excised specimen demonstrating histological features identical to those of the removed right kidney. The patient was recommenced on maintenance chlorambucil (5 mg daily) and prednisolone (10 mg daily) and has remained well without further recurrent disease for the last 14 months (> 5 years after the right nephrectomy).

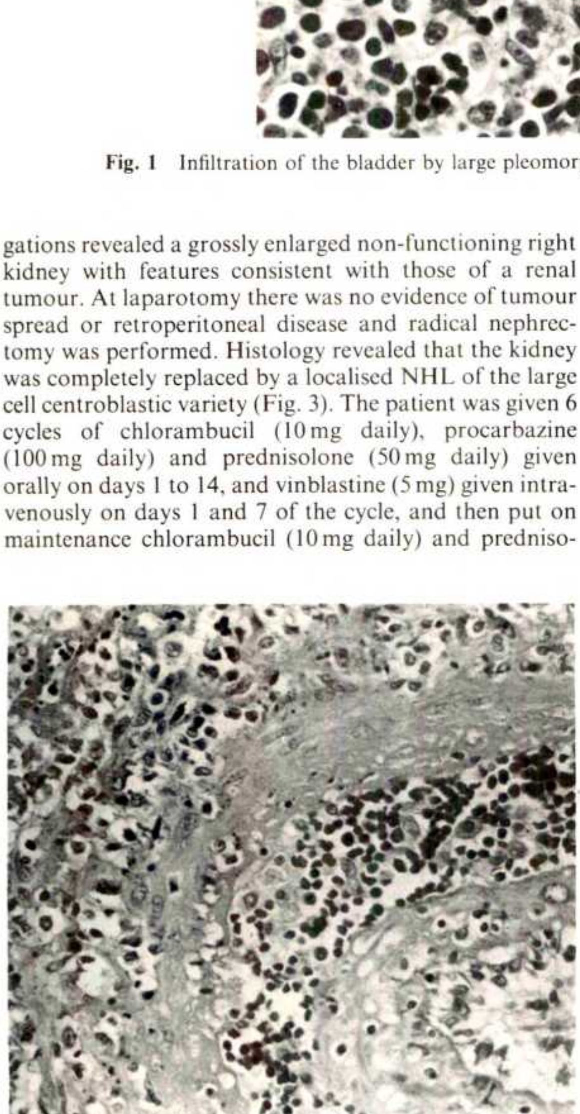

Fig. 2 Infiltration of the prostatic stroma by large pleomorphic lymphoid cells (diffuse large cell NHL). (H and E × 240).

Discussion

Involvement of the urinary tract by NHL is uncommon. Post mortem examinations have demonstrated that 10% of patients with NHL have infiltration of the urinary tract, but this may manifest itself as urological symptoms in less than 1% of cases (Watson *et al.*, 1949; Weimar *et al.*, 1981).

Primary presentation of NHL as a lymphoma of bladder or prostate is exceedingly rare and less than 50 cases have been documented in each organ (Chaitin *et al.*, 1984; Lewi *et al.*, 1984). Cases 1 (bladder lymphoma) and 2 (lymphoma of prostate) represent an interesting variant of apparently primary extra-nodal NHL. The prognosis of patients who present with either prostatic or bladder lymphoma as the initial manifestation of their tumour is variable and dependent upon the histological

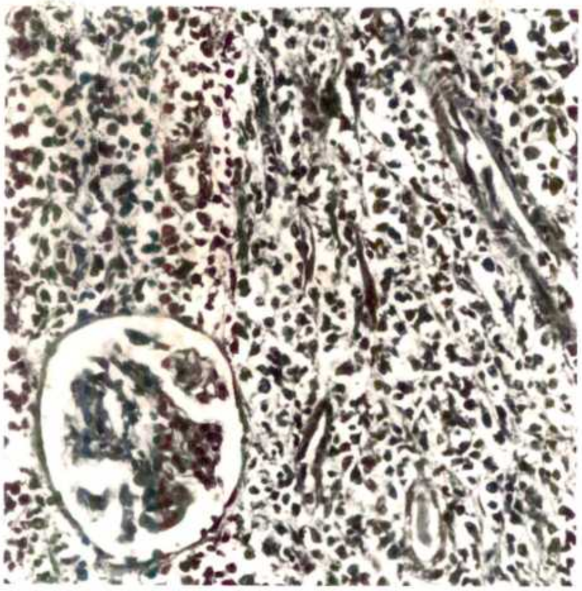

Fig. 3 Infiltration of the interstitium of the kidney by a pleomorphic lymphoid population. A surviving glomerulus is seen and a few atrophic renal tubules remain (large cell controblastic NHL). (H and E × 180).

nature of the lymphoma, the subsequent extra-urinary tract spread and response to treatment. For patients with a bladder lymphoma, Chaitin *et al.* (1984) quoted a 50% 5-year survival rate, but in those with a lymphoma of the prostate survival appears to be poorer, with a median survival of 13 months being observed and few patients surviving 5 years after diagnosis (Melchior *et al.*, 1974; Hampel *et al.*, 1977; Elisei *et al.*, 1979; Lewi *et al.*, 1984).

The most common form of urogenital involvement by NHL is direct infiltration of the kidney by a retroperitoneal mass with associated renal parenchymal and ureteric obstruction (Watson *et al.*, 1949; Weimar *et al.*, 1981; Whitmore *et al.*, 1982).

Whilst renal infiltration by NHL is common, a localised renal lymphoma is exceedingly rare, and in a review of 2360 cases of primary renal tumours over a 60-year period, localised renal lymphoma accounted for less than 0.5% of cases (Farrow *et al.*, 1968). Previously documented cases were identical to the case described, in that the tumour was localised to the kidney and not part of a generalised infiltrating retroperitoneal mass. Five-year survival in localised renal lymphoma is rare, and of all cases documented there have been only two patients who survived longer than 5 years following nephrectomy; with the advent of better chemotherapeutic regimes, superior survival figures may be expected.

Whilst it is unlikely that the urogenital lymphoma is the primary site of origin of NHL, it has been observed that in 15% of cases the first manifestation of the disease is extra-nodal and includes sites such as the gastro-intestinal tract, nasopharynx and spleen (Lennert, 1981). Involvement of the genito-urinary tract, whether sufficient to cause presentation or found incidentally, often represents evidence of widespread disease. Patients with urogenital lymphoma are best treated by a combination of surgery, radiotherapy and chemotherapy (Watson *et al.*, 1949; Weimar *et al.*, 1981; Whitmore *et al.*, 1982; Lewi *et al.*, 1984).

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The Authors

H. J. E. Lewi, FRCS, Senior Registrar in Urology.
I. D. S. Stewart, MB,ChB, SHO in Urology.
M. Seywright, MB,ChB, Registrar in Pathology.
S. Fleming, MB,ChB, Registrar in Pathology.
R. F. Deane, FRCS, Consultant Urologist.
K. F. Kyle, FRCS, Consultant Urologist.

Requests for reprints to: H. J. E. Lewi, Department of Urology, Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ER.

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Immunohistochemical Analysis of the Human Bladder

R. A. GARDINER, G. J. SEYMOUR, M. F. LAVIN, G. M. STRUTTON, E. GEMMELL and G. HAZAN

Departments of Surgery, Social and Preventive Dentistry and Pathology, University of Queensland, Brisbane, Australia

Summary—An immunohistochemical profile of cells in the mucosa and lamina propria of adult human bladders is described. Urothelial cells were HLA-DR-ve, ACP+ve and ATPase-ve. All lymphocytes in this layer were of the suppressor/cytotoxic T subgroup and dendritic cells with an identical phenotype to Langerhans cells were seen. In the lamina propria most lymphocytes were of the suppressor/cytotoxic type with some helper/inducer cells. An occasional natural killer cell and Langerhans cell was identified and large macrophage cells with a common phenotype to antigen presenting interdigitating (ID) cells were noted. Fibronectin staining was dense in the vicinity of basement membranes merging to form fine interconnecting latticework-like structures elsewhere in the lamina propria.

Development of the techniques of lectin histochemistry, and more specifically immunohistochemistry, have permitted superimposition of functional information on to the architectural detail provided by conventional histology. In the urinary tract most attention has been addressed to the urothelial cell, and in particular to blood group antigens A, B and O(H) with changes of expression of these (as well as other blood group antigens) with neoplastic transformation (Bergman and Javadpour, 1978; Lange *et al.*, 1978; Gunter *et al.*, 1983; Rearden *et al.*, 1983; Summers *et al.*, 1983). Other epithelial cell antigens have been identified on urothelial cells including urothelial membrane-associated antigen (UMA) (Hodges *et al.*, 1982), luminal epithelial antigen (LEA) (Nathrath *et al.*, 1979) and epithelial membrane antigen (EMA) (Pocock *et al.*, 1983). However, despite close scrutiny of urothelial cell antigen status, little attention has been paid to accompanying lymphocyte and macrophage populations.

In recent years, with the advent of monoclonal antibodies, it has become possible to identify T-lymphocytes (OKT3 positive) from B-lymphocytes and to distinguish between helper/inducer T-cells (OKT4 positive) and suppressor/cytotoxic T-cell (OKT8 positive) subsets in both normal and disease situations (Janossy *et al.*, 1980; Bach *et al.*, 1981; Selby *et al.*, 1981; Poulter *et al.*, 1982; Mishra *et al.*, 1983; Poppema *et al.*, 1983). In addition to T-lymphocyte characterisation, it is becoming increasingly evident that cells of the monocyte/macrophage series form a heterogeneous population (Humphrey, 1981; Poulter *et al.*, 1982; Seymour *et al.*, 1983). This is illustrated by interdigitating (ID) cells of T-dependent areas of lymphoid tissues which are capable of antigen presentation (Balfour *et al.*, 1981; Humphrey, 1981) and clearly are distinct from phagocytic macrophages. Accordingly, information is accumulating that these functionally distinct groups of cells express different phenotypes (Poulter, 1983). Although both macrophage cell types are HLA-DR positive, ID cells exhibit large amounts of adenosine triphosphatase (ATPase) on their membranes yet contain low levels of lysosomal enzymes, but phagocytic macrophages are intensely acid phosphatase (AcP) positive and are equivocal in their staining for ATPase.

Not only is it possible now to identify these subpopulations of T-cells and macrophages but it is also feasible to analyse their microenvironments *in situ* (Janossy *et al.*, 1981; Selby *et al.*, 1981; Poulter *et al.*, 1982). An important component of the extra-

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Table 1 Details of Patients

Patient number	*Gender*	*Age*	*Drug therapy*	*Type of biopsy*	*Procedure*
1	M	74	1. Beclamethasone diopropionate metered aerosol spray; 2 puffs 6-hourly 2. Oxazepam; 15 mg bd 3. Salbutamol metered aerosol spray; 2 puffs 4-hourly	Open	Millin's prostatectomy
*2	M	69	1. Potassium chloride (sustained release); 1200 mg nocte 2. Trimethoprim with sulphamethoxazole; 160-800 mg bd	Open	Millin's prostatectomy
3	M	78	Methyclothiazide; 5 mg mane	Closed	Cystoscopy with retrograde pyelogram for radiolucent stone
*4	M	73	1. Frusemide; 40 mg mane 2. Potassium chloride (sustained release); 600 mg tds 3. Trimethoprim with sulphamethoxazole; 160-800 mg bd 4. Verapamil hydrochloride; 120 mg tds	Open	Millin's prostatectomy
5	F	34	Nil	Closed	Cystoscopy for sensory urgency with frequency
6	F	77	Nil	Closed	Cystoscopy and urethral dilatation

* A catheter was indwelling prior to biopsy, but specimens were selected from parts of the bladders which were macroscopically normal.

cellular microenvironment is fibronectin. This glycoprotein, present in plasma in a soluble form in which it is opsonic for reticuloendothelial phagocytosis (Saba and Jaffe, 1980), as an insoluble variant forms a latticework of filamentous arrays as a component of extracellular matrix. Fibronectin is produced by most cells (Reid and Coppleson, 1983) and is postulated to be important in cell adhesion (Yamada and Olden, 1978), migration (Critchley *et al.*, 1979) and differentiation (Linder *et al.*, 1975). In general, fibronectin co-distributes with type III collagen (IIIC) and it has been suggested that histological "reticulin" fibres demonstrated by silver impregnation (Timpl *et al.*, 1977; Stenman and Vaheri, 1978) are compound structures containing fibronectin, IIIC and at least one other non-collagenous glycoprotein (Unsworth *et al.*, 1982). The distribution of fibronectin and its relationship to resident macrophage populations in the human bladder is unknown. Fibronectin patterns have been shown to be disrupted considerably with neoplastic changes *in vitro* (Reid and Coppleson, 1983). Consequently, if similar disruptions can be demonstrated *in situ* by immunohistochemistry, they might indicate imminent invasion by malignant cells in bladder cancer and thus together with T-cell macrophage characterisation be of predictive value, indicating host response to a particular tumour.

The present study was undertaken to identify the various T-cell and macrophage subpopulations and to determine the pattern and distribution of fibronectin in the human bladder.

Materials and Methods

Tissue and selection

Bladder wall biopsies (three open; three closed) were obtained from six patients (four males and two females) in whom the bladders appeared normal cystoscopically. These patients had an age range between 34 and 78 years and pre-operatively all had uninfected urine with normal urinary cytology (Table 1). In each instance one biopsy specimen was sent for routine histology (formalin fixed, paraffin embedded with sections stained by haematoxylin and eosin) and another immediately adjacent specimen was sent for immunohistochemical studies.

The specimens for immunohistochemical examination were embedded in OCT® (Lab-tek, USA) compound and quenched in liquid nitrogen. Six micron cryostat sections were cut, air dried for 2 h at room temperature, fixed in chloroform-acetone for 5 min at room temperature, then stored at −20°C until used.

Immunofluorescence and immunoperoxidase

Indirect immunofluorescence and immunoperoxidase labelling was performed as previously described (Poulter *et al.*, 1983; Seymour *et al.*, 1983). Briefly, sections were incubated with first layer antibodies for 30 min at room temperature, washed in phosphate buffered saline (PBS) pH 7.2 for 15 min, then incubated with second layer conjugated fluorescein isothiocyanate (FITC) or peroxi-

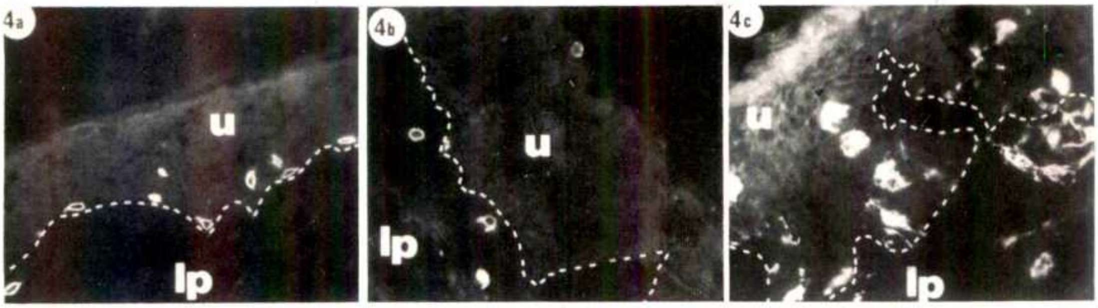

Fig. 4 (a) Immunofluorescence staining showing T3 +ve intra-urothelial lymphocytes. u—urothelium, lp—lamina propria. (Original magnification ×250). (b) Immunofluorescence staining showing T4 +ve (helper/inducer) lymphocytes mainly in the lamina propria (lp) while the urothelium (u) is essentially negative. (Original magnification ×250). (c) Immunofluorescence staining showing T8 +ve intraurothelial lymphocytes. Most cells are within the urothelium (u) although some T8 +ve cells can be seen in the lamina propria (lp). (Original magnification ×250).

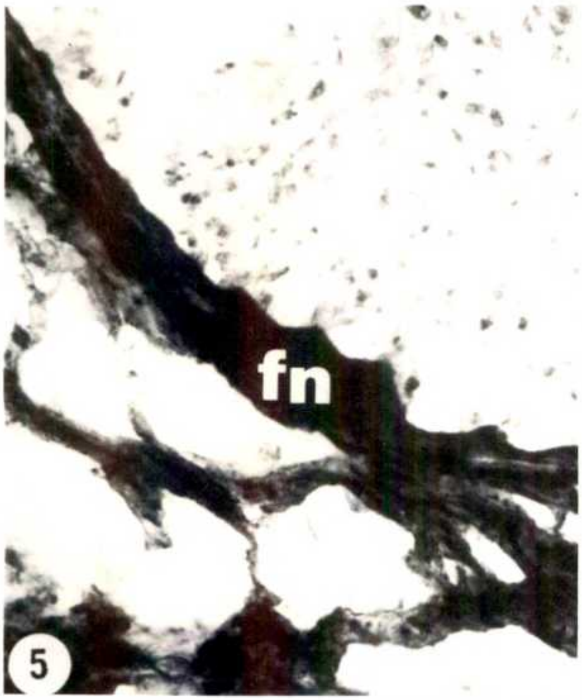

Fig. 5 Immunoperoxidase staining using a monoclonal antifibronectin antibody. The fibronectin (fn) can be seen forming a dense band along the basement membrane. (Original magnification ×400).

+ve, T8 +ve, T4 −ve). Additionally, T-cells were found in the lamina propria of the bladder and included both T4 +ve and T8 +ve subpopulations, although the latter predominated. The role of these T8 +ve lymphocytes is speculative. Presumably, such cells function similarly to T8 +ve lymphocytes in epithelia elsewhere, probably being cytotoxic to urothelial cells altered antigenically and as such contribute to the maintenance of urothelial homeostasis. Alternatively, these cells may have a suppressor function and hence play an important role in interaction between mucosal and systemic immune systems (Selby *et al.*, 1981). This is consistent with the concept of the urothelial surface being an integral component of the mucosal immune system. Additionally, it is possible that both roles are fulfilled by this subpopulation of T-cells because it is not possible to distinguish between suppressor and cytotoxic components with these monoclonal antibodies.

Recently, both morphological and functional heterogeneity within the monocyte/macrophage population has been recognised (Humphrey, 1981; Poulter, 1983). It is now accepted that lymphocytes cannot respond to "raw" antigen and it is the role of some members of the macrophage family to "process" antigenic material and "present" appropriate epitopes that can be recognised by lymphoid populations. Macrophages inducing T-cell stimulation express high concentrations of HLA-DR antigens (Poulter, 1983). The predominating macrophage type identified in the lamina propria in this study was the HLA-DR +ve (as well as ATPase +ve, AcP −ve) macrophage. This cell type shares a common phenotype with interdigitating cells of regional lymphoid tissue, as well as with those macrophages found lining the epithelium of intestine and it is tempting to speculate that these cells resident in the bladder are antigen presenting too. However, in the absence of functional assays, such an interpretation cannot be attributed to these cells unequivocally.

The discovery of HLA-DR +ve ATPase +ve OKT6 +ve "dendritic cells" within the urothelium is also interesting. These cells have a phenotype identical to Langerhans cells (LC) which have a surveillance role in epidermis and their presence

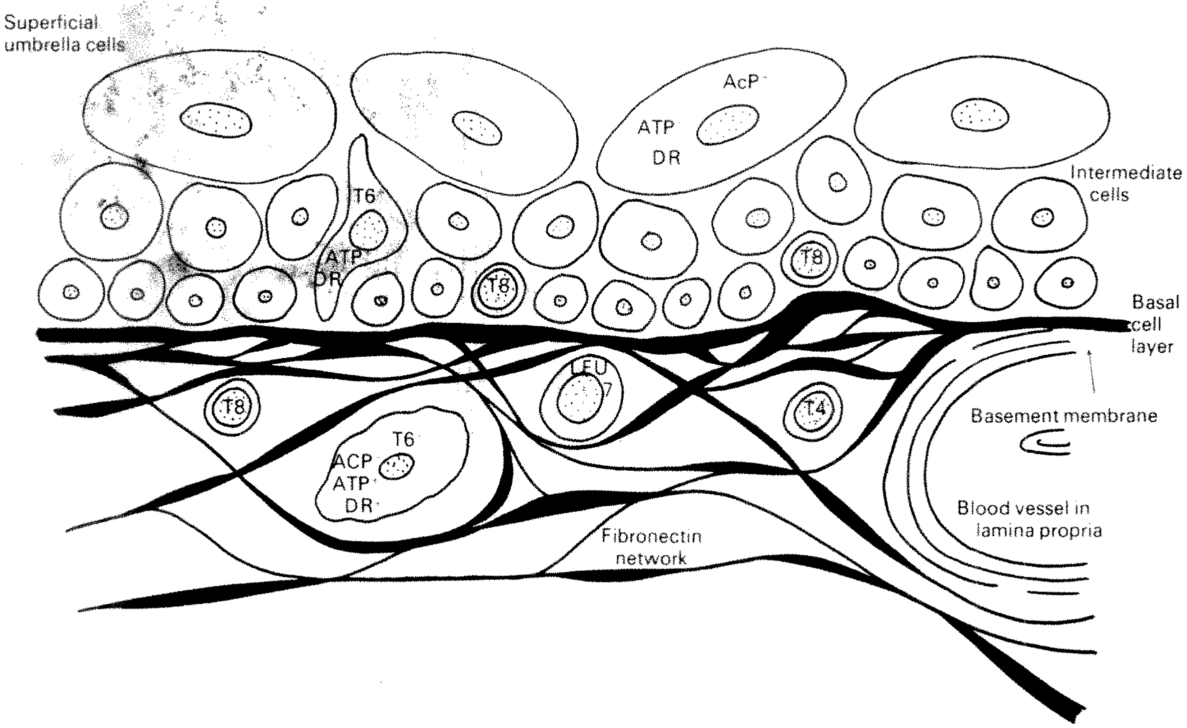

Fig. 6 Diagrammatic representation.

within the urothelium is indeed intriguing. Epidermal LC have been shown to have a definite antigen presenting role and it seems likely that bladder or urothelial LC would function similarly.

The lack of HLA-DR staining of the urothelium is consistent with staining of other mucosal surfaces. However, a change in HLA-DR expression by epithelial cells outside the urinary tract is not uncommon in association with cell-mediated immune reactions (Lampert *et al.*, 1981).

In skin and kidney, immunochemistry at an ultrastructural level has suggested that fibronectin is present on epithelial cell plasma membranes adjacent to basal lamina (Couchman *et al.*, 1979; Dixon and Burns, 1982). The limited resolution afforded by light microscopy in the present study localised fibronectin patterns as filamentous arrays forming latticework-like networks about cells in the extracellular tissue merging imperceptibly with basement membranes. Since basement membrane disruption is the *sine qua non* of invasion with malignancy, study of fibronectin patterns in similar instances might prove rewarding.

In this report our findings using immunohistochemical techniques for studying human bladders are described. Cell phenotype characterisation together with fibronectin labelling have identified the immunohistochemical pattern. It is intended that this study should serve as a useful reference in applying this mode of investigation of pathological conditions involving the bladder.

Acknowledgement

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The Authors

R. A. Gardiner, FRCS, FRACS, Senior Lecturer in Urology.

G. J. Seymour, BDS, MDSc, PhD, MRCPath, Associate Professor in Social and Preventive Dentistry.

M. F. Lavin, BSc, PhD, Associate Professor in Biochemistry.

G. M. Strutton, BSc, FRCPA, Senior Lecturer in Pathology.

E. Gemmell, BSc, Research Assistant, Department of Dentistry.

G. Hazan, Final year medical student, University of Sydney.

Requests for reprints to: R. A. Gardiner, Department of Surgery, University of Queensland, Clinical Sciences Building, Royal Brisbane Hospital, Herston, Queensland 4029, Australia.

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The Value of Aspiration Cytology in the Definitive Staging of Bladder Carcinoma

L. LUCIANI, F. PISCIOLI, T. PUSIOL and P. SCAPPINI

Departments of Urology and Pathology, S. Chiara Hospital, Trento, Italy

Summary—Aspiration cytology is a simple, accurate and minimally invasive procedure in staging urological neoplasms. Percutaneous fluoroscopy-guided fine needle aspiration biopsy of 99 lymph nodes was performed in 30 patients with bladder carcinoma and 62 lymph node chains were evaluated. Aspiration biopsy is more accurate and specific than lymphography in the pre-operative staging of the neoplasm and represents a useful diagnostic procedure for the staging of bladder carcinoma.

Accurate staging of bladder carcinoma is essential both for planning appropriate therapy and for determining the prognosis of the disease. There are, however, many pitfalls (Schmidt and Weinstein, 1976) and it is generally agreed that the more the neoplasm penetrates the bladder wall the less accurate is the pre-operative staging. Jewett (1952) stated that tumours that have infiltrated more than 50% of the muscle layer of the urinary bladder have already metastasised. An error rate of 34% in patients clinically staged A or B1, increasing to 50% if clinical staging was B2 or C, was reported by Marshall (1952). In the series of patients reported by Kenny *et al.* (1970), 35 (33%) were undestaged and 24 (23%) overstaged. Varkarakis *et al.* (1974) found agreement between clinical stage O,A and B1 and pathological findings in 86% of cases; their understaging rate was 9% and the overstaging rate 5%. Richie *et al.* (1975) examined 134 patients with bladder carcinoma and concluded that 40% were clinically understaged and 26% overstaged.

One of the main sources of error in the staging of deeply invasive bladder carcinoma is inadequate evaluation of the regional lymph nodes and numerous diagnostic techniques have been proposed to deal with this problem. The purpose of this study was to determine the value of aspiration cytology in the staging of bladder carcinoma and to compare the accuracy of this minimally invasive procedure with that of lymphography.

Materials and Methods

Following standard bipedal lymphangiography, fluoroscopy-guided fine needle aspiration cytology of 99 lymph nodes was performed in 30 patients with bladder carcinoma. The biopsies were performed with a long-bevelled, modified Chiba needle with side holes (Luciani and Piscioli, 1983). The technique has been described by Wallace *et al.* (1977), Zornoza *et al.* (1977), Gothlin (1978) and Luciani and Piscioli (1983). The nodes were aspirated regardless of the preliminary lymphographic diagnosis. The cytological and lymphographic diagnoses were classified as positive or negative and no "suspected" category was used. Pelvic dissection was performed in all patients in the course of surgical procedures (exploratory laparotomy, urinary diversion, partial and radical cystectomy).

The pathological stage was determined according to the TNM system (UICC, 1978).

Results

The site of the nodes, the cytological, lymphographic and histological findings, surgical stage and treatment for each patient are summarised in Table 1.

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Table 1 Correlation between Aspiration Cytology, Lymphography and Histology in the Staging of Bladder Carcinoma

Number of Patients	*Cytological findings of the nodes biopsied*				*Lymphographic and histological findings of the nodes removed*				Treatment	Pathology
	EI	*CI*	*II*	*Ob*	*EI*	*CI*	*II*	*Ob*		
1				R (+)				R1 (1+)*	RC	pT2 N1 M0
2				R (−)				R1 (−)*	RC	pT2 N0 M0
3	R (−) L (−)				R6 (−) L4 (−)*				RC	pT2 N0 M0
4	R (−) L (−)				R5 (−)* L4 (−)*		L3 (−)		RC	pT4 N0 M0
5	R (−) L (−)	R (−)			R4 (−)	R3 (−)			PC + total nephrouret. CT	pT1 N0 M0
6	R (−) L (−)			L (+)	R4 (−) L5 (−)			L6 (4+)	Biopsy	pT3 N2 M0
7	L (−)		L (−)	L (−)	R4 (−)* L7 (−)				PC	pT3 N0 M0
8	R (−)		R (−)	R (−) L (−)	R3 (−) L1 (−)	R2 (−)			RC	pT4 N0 M0
9	R (−) L (−)		L (−)	L (−)	L1 (1+)*				Biopsy	pT3 N1 M0
10	R (−) L (−)	R (−)	R (−)	R (−)	R6 (−) L1 (−)			R1 (−) L2 (−)	RC	pT3 N0 M0
11	R (−) L (−)	R (−)	R (−)	R (−)	R2 (−)				RC	pT1 N0 M0
12	R (−) L (−)	L (−)	R (−) L (−)		R11 (−) L6 (−)			R3 (−)	RC	pT2 N0 M0
13	R (−) L (−)	R (−) L (−)			R4 (−)			R3 (−)	PC	pT2 N0 M0
14	R (+) L (−)	R (−)	R (+) L1 (−)		R1 (1+)* L1 (−)*		L1 (−)		Biopsy	pT3 N1 M0
15	R (−) L (−)			R (−) L (−)	R2 (−) L3 (−)			R4 (−) L6 (−)	RC	pT2 N0 M0
16		L (+)				L2 (2+)*			Biopsy	pT4 N2 M0
17	R (−) L (−)		L (−)	R (−)	R9 (−) L4 (−)		R4 (−) L1 (−)	R1 (−)	RC	pT4 N0 M0
18	R (−) L (−)	L (−)		R (−)	L6 (−)*			L5 (−)	RC	pT3 N0 M0
19	R (−) L (−)			R (−) L (−)	R7 (−) L6 (−)			R4 (−) L6 (−)	RC	pT2 N0 M0
20	R (−) L (−)	R (−) L (−)	R (−)	R (−) L (−)	R5 (−)*			R2 (−)	Biopsy	pT4 N0 M0
21	R (−) L (−)	L (−)			L2 (−)			L6 (−)	RC	pT3 N0 M0
22				R (−)	R10 (−) L5 (−)			R3 (−)	RC	pT3 N0 M0
23	R (−) L (+)			L (−)	R4 (−) L5 (3+)		L1 (−)	L1 (−)	PC	pT4 N1 M0
24	R (−) L (−)				R5 (−) L7 (−)				RC	pT3 N0 M0
25	R (−)				R1 (−)*				PC	pT2 N0 M0
26	R (−) L (−)			R (−) L (−)	L4 (−)		R3 (−)	L9 (−)	PC	pT2 N0 M0
27	R (−) L (−)			R (−)	R14 (−) L3 (−)			R5 (−)	RC	pT3 N0 M0
28	R (−) L (−)			R (−) L (−)	R8 (−) L4 (−)			L3 (−)	RC	pT3 N0 M0
29	R (−) L (−)			R (−) L (−)	R2 (−) L2 (−)			R7 (−) L1 (−)	RC	pT3 N0 M0
30	R (−) L (−)			R (−)	R1 (−)			R2 (−)	RC	pT3 N0 M0

R = Right (−) = Negative cytology N(−) = Number of nodes examined (negative histology)
L = Left (+) = Positive cytology N(N +) = Number of nodes examined (number of positive nodes)
* = Positive lymphogram PC = Partial cystectomy EI = External iliac chain RC = Radical cystectomy CI = Common iliac chain II = Internal iliac chain Ob = Obturator chain

Table 2 Accuracy, Sensitivity and Specificity of Lymphography and Aspiration Cytology in Staging of Bladder Carcinoma (30 Patients)

	Accuracy (%)	*Specificity* (%)	*Sensitivity* (%)
Lymphography	70	71	66
Aspiration cytology	96	100	83

Table 3 Accuracy, Sensitivity and Specificity of Lymphography and Aspiration Cytology in Determining the Status of Pelvic Nodes in 30 Patients with Bladder Carcinoma

	Accuracy (%)	*Specificity* (%)	*Sensitivity* (%)
Lymphography	85	87	60
Aspiration cytology	98	100	83

Ninety-nine lymph nodes were aspirated. Cytological material from six nodes contained malignant cells. Sixty-two nodal chains were histologically evaluated. In the staging of the tumour, aspiration cytology and lymphography gave accuracy rates of 96 and 70%, sensitivity rates of 83 and 66%, and specificity rates of 100 and 71% respectively (Table 2).

In determining the status of a single pelvic node, aspiration cytology was compared with lymphography and showed accuracy rates of 98 versus 85%, sensitivity rates of 83 versus 60% and specificity rates of 100 versus 87% respectively (Table 3). No significant complications were encountered.

Discussion

Lymphography is often used to determine the degree of lymph node involvement in bladder carcinoma but its accuracy rate has aroused controversy. Collard and Timmermans (1973) stated that lymphography is useful only in cases of testicular tumours and has little value in renal, ureteric and vesical neoplasms because of the anatomical distribution of the lymph nodes and the non-specific character of the lacunar appearance of the metastatic nodes.

Grasset and Navratil (1973) compared the lymphographic and histological findings in 25 patients with bladder carcinoma and found a 60% correlation, with 30% false positive and 10% false negative results. Because of the high percentage of error these authors opposed the use of lymphography in the staging of bladder carcinoma.

Turner *et al.* (1976) performed lymphography of the pelvic nodes in 237 patients with bladder carcinoma and histological examination in 65. They reported a correlation between these two procedures in 90% of the cases, with 9% false negative results. Since the 5-year survival rate was about 40% in the negative cases and 2 to 3% in the positive ones, the authors concluded that a positive lymphogram is associated with a poor prognosis, especially when nodal involvement is bilateral or extends to para-aortic nodes. Thus in the study by Turner *et al.* (1976), lymphography plays a fundamental part in the management of patients with infiltrating bladder carcinoma, in the TNM categorisation of the disease and in the selection of appropriate treatment.

Essed and Mulder (1979) noted agreement in 72%, false positive results in 11% and false negative results in 17% of 90 lymphograms compared with the histological findings. They claimed that lymphangiography does not distinguish between N1 and N2 cases. This implies that the former may be confused with the latter and that some patients might be denied adequate therapy. For these reasons Essed and Mulder (1979) were not in favour of therapy based upon lymphographic findings.

Juimo *et al.* (1982) compared the reported values of sensitivity (85%), specificity (84%) and accuracy (84%) with those obtained in their own series of 50 patients: sensitivity 43%, specificity 100% and accuracy 84%. They also believed that lymphographic results could be improved by the use of fine needle aspiration cytology.

The conclusion to be drawn from these reports is that lymphography is unreliable in the staging of bladder carcinoma and only histological examination of surgically removed lymph nodes can provide accurate information on their status. Lymphadenectomy has a low morbidity rate. Aspiration cytology is a simple, minimally invasive diagnostic procedure for determining the status of the pelvic nodes and a high percentage of patients with penile, prostatic or bladder carcinoma can be accurately staged with minimal morbidity. Aspiration cytology was originally used to confirm positive lymphographic findings or to evaluate abnormal or equivocal lymphograms (Dan *et al.*, 1982a and b).

Subsequently, since lymphography has been found to be inaccurate in determining the nodal in-

Table 4 Aspiration Cytology in the Staging of Bladder Carcinoma (Review of the Literature)

Authors	*Total patients*	*Patients with bladder carcinoma*	*Total patients with satisfactory specimens*	*Patients with positive cytology*	*Patients with negative cytology*	*Total patients with histological control*
Gothlin (1976)	45	NS	37	—	—	11
Zornoza *et al.* (1977)	17	2	14	—	—	8
Gothlin (1978)	107	NS	93	58	35	49
Wein *et al.* (1979)	26	8	23	5	18	17 (FN 7)
Rothenberger *et al.* (1981)	126	45	NS	10	NS	27
Wajsman *et al.* (1982b)	57	21	41	15	26	26 (FN 7) (FP 2)
Wajsman *et al.* (1982a)	100	32	83	20	63	50 (FN 15) (FP 1)
Luciani *et al.* (1983)*	14	14	14	4	10	14
Boccon Gibod *et al.* (1984)*	54	54	47	13	34	38 (FN 7)

FN = False negative; FP = False positive; NS = Not specified
* Series including only patients with bladder carcinoma

volvement of urological malignancies, the use of percutaneous fine needle aspiration biopsy has been extended to lymphographically "normal" lymph nodes (Göthin and Høiem, 1981).

The positive cytological results may provide a rational basis for therapy. Negative cytological data are uninformative and do not generally affect clinical management (Wajsman *et al.*, 1982a and b).

In reviewing the use of aspiration cytology in the staging of urological neoplasms (Wallace *et al.*, 1977; Zornoza *et al.*, 1977; McIntosh *et al.*, 1979; Correa *et al.*, 1981; Efremidis *et al.*, 1981; Göthlin *et al.*, 1981; Dan *et al.*, 1982a and b; Khan *et al.*, 1983; Luciani and Piscioli, 1983; Nadalini *et al.*, 1983), it is evident that only single cases or small series of bladder carcinoma have been reported and it is not possible to establish the accuracy, sensitivity and specificity of aspiration cytology in the pre-operative staging of large series of patients with bladder carcinoma. Furthermore, there are no reports of a comparison between lymphography and aspiration cytology in establishing the status of the lymph nodes and the stage of bladder carcinoma (Table 4). The 30 patients in the present study form the largest reported series of fine needle aspiration biopsies with histological control in patients with bladder carcinoma.

In this study, aspiration biopsy showed higher accuracy, sensitivity and specificity rates than lymphography in the staging of bladder carcinoma (96 versus 70%; 83 versus 66%; 100 versus 70% respectively).

In our experience lymphography is insufficiently accurate in determining lymph node status (Table 3) and we recommend aspiration biopsy of all lymph nodes opacified by lymphography regardless of the lymphographic findings.

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The Authors

L. Luciani, MD, Director, Department of Urology.
F. Piscioli, MD, Assistant, Department of Pathology.
T. Pusiol, CT, Assistant, Department of Pathology.
P. Scappini, MD, Assistant, Department of Urology.

Requests for reprints to: L. Luciani, Department of Urology, S. Chiara Hospital, 38100 Trento, Italy.

Addendum

Steg and Boccon-Gibod (1985) and Wajsman (1985) have recently confirmed our data and demonstrated the usefulness of lymph node aspiration cytology in the pre-operative staging of patients with invasive bladder carcinoma.

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Methotrexate, Cisplatin and Carboplatin as Single Agents and in Combination for Metastatic Bladder Cancer

R. T. D. OLIVER, H. K. KWOK, W. J. HIGHMAN and J. WAXMAN

The London and St Bartholomew's Hospital Medical Colleges and Institute of Urology, London

Summary—A review of 78 previously untreated patients with bidimensionally measurable metastatic bladder cancer who were entered into a series of studies of cytotoxic chemotherapy has shown that complete response occurred in 1 of 23 patients receiving methotrexate, none of 15 receiving cisplatin, none of 20 receiving the platinum analogue carboplatin and 3 (2 with histological confirmation) of 20 receiving methotrexate in combination with cisplatin. WHO/UICC performance status 3 and 4, though a prediction of lower response, did not provide a means for excluding patients who might benefit from chemotherapy. Studies using serial cytology showed that 5 of 8 responders according to standard criteria had complete loss of malignant cells from the urine compared with none of 10 non-responders and there was a suggestion that duration of response was longer in those whose urine was negative for malignant cells than in those which remained positive.

Radiotherapy leads to the complete disappearance of bladder tumour masses in more than 30% of patients, half of whom remain disease-free (Blandy *et al.*, 1980). Patients with terminal metastatic bladder cancer have benefited, in a palliative sense, from cytotoxic chemotherapy (Oliver *et al.*, 1984) and the two most consistently active single agents remain methotrexate and cisplatin. There is no suggestion, however, that complete response and long-term cure are achieved with these single agents. Recently there has been increasing evidence that combinations involving methotrexate and cisplatin (Carmichael *et al.*, 1985; Stoter *et al.*, 1985), and in some centres the addition of vinblastine with or without adriamycin, may produce a real increase in the incidence of histologically documented complete responses (Harker *et al.*, 1983; Sternberg *et al.*, 1985).

We report the results of a methotrexate/cisplatin combination and compare this with single agent studies which have been performed previously.

Patients and Methods

Two groups of patients were studied; all had biopsy-proven invasive primary transitional cell carcinoma of the bladder, ureter or renal pelvis. The first group had measurable metastases in lymph nodes, lung or liver confirmed histologically by fine needle biopsy where possible and the second group had symptomatic bone metastases.

Serial urine cytology has been performed on some of these patients and in patients from two other previously reported studies (Oliver, 1982; Oliver *et al.*, 1984).

Chemotherapy Regimes

(a) Methotrexate

Details of the patients and regimen have been reported elsewhere (Oliver *et al.*, 1984).

(b) Cisplatin

These patients were treated as part of a group study, details of which have been published by Oliver *et al.* (1981). The standard dose was 50 mg/m^2 every 3 weeks.

Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

Table 1 Chemotherapy in Previously Untreated Patients with Measurable Metastatic Transitional Cell Carcinoma

	Number of cases	*Complete response*	*Duration (months)*	*Partial response*	*Median duration survival (months)*
Methotrexate	23 (9)*	1	12	9 (1)*	6
Cisplatin	15	0	—	3	5
Carboplatin	20 (2)*	0	—	2 (1)*	5
Methotrexate plus cisplatin	20 (1)*	3	6, + 12, + 12	6 (1)*	6

*Number of additional patients receiving specific chemotherapy as second-line treatment.

(c) Carboplatin

These patients were treated as part of an MRC Phase 2 trial, details of which have been published elsewhere. The dose was 400 mg/m² in 500 ml 5% Dextrose over 1 h, though doses were adjusted on the basis of age and glomerular filtration rate (Medical Research Council, 1985).

(d) Methotrexate and Cisplatin

Methotrexate 60 to 80 mg/m² was given by intravenous bolus followed 24 h later by folinic acid 15 mg (× 1). Intravenous hydration was begun immediately after the methotrexate and cisplatin 60 to 80 mg/m² were given, starting 24 h after the methotrexate. This regime was repeated every 3 weeks but on day 10, provided that haematology and renal function were within normal limits, methotrexate 30 to 50 mg/m² iv was given. After four courses, patients who responded were maintained on methotrexate 75 to 100 mg 2-weekly for the first 6 months and 3-weekly from 6 to 12 months.

Assessment of Response

All patients were assessed for response. Treatment was continued until there was evidence of disease progression; in the event of non-response it was stopped when the side effects of treatment were worse than the symptoms of the disease.

Conventional methods were used for assessing response of patients with measurable metastases (Yagoda, 1981), although an additional category of minimal response was defined on the basis of sustained (> 2 months) improvement in tumour measurement not satisfying standard criteria or reduction in bone pain and improved performance status.

Results

Ninety-five patients have been studied, 78 with measurable metastases (Table 1). Response to cisplatin or carboplatin was less impressive than response to methotrexate or the combination of methotrexate and cisplatin. Although there was no difference in the total frequency of response to methotrexate on its own or when combined with cisplatin (44% vs. 45%, $P = \mathrm{NS}$), there were slightly more complete responses (4% vs. 15%) and the patients showing partial responses were closer to complete response (Fig.). Two of the complete responders to methotrexate and cisplatin had histology taken from the areas of previous positive metastatic soft tissue disease to confirm the response; an additional partial responder to this combination had histologically proven complete response in a soft tissue mass but residual tumour in the bladder which was removed at cystectomy; the patient is now alive and disease-free at 12 months.

Few of the patients receiving second-line treatment showed a response. One patient with histologically proven para-aortic lymph node metastases responded to methotrexate for 10 months, then progressed, then responded to carboplatin for 15 months and then on progression responded a third time to methotrexate and carboplatin for 3 months.

There was no significant difference in the frequency of response when patients were assessed by principal site of measurable disease (Table 2). Although only 1 of 17 patients with bone metastases had a change on bone scan, the incidence of palliation as measured by reduction in bone pain

Table 2 Influence of Principal Site of Disease on Response to Chemotherapy

	Number of cases	*Complete response*	*Partial response*	*Minor response*
Lymph node	33	1	9	3
Lung	27	1	7	1
Liver	9	—	2	—
Soft tissue	11	2	2	2
Bone	17	—	1	5

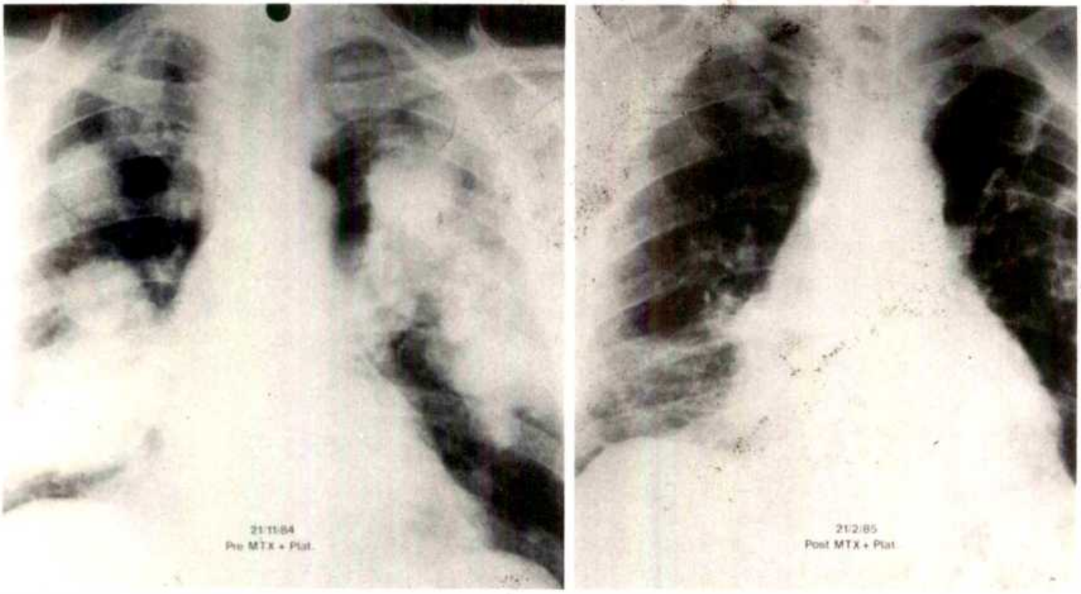

Fig. Partial response to methotrexate and cisplatin. Patient remains in remission at 9 months.

and improved performance status was as good in this group as in those with measurable metastases.

Although WHO/UICC performance status 3 and 4 was a significant factor in determining survival and the frequency of response, which was lower than in patients with a good performance status (Table 3), the three responses in bedridden moribund patients produced virtually symptom-free periods of 4, 9 and 9 months. In each case there was symptomatic evidence of response within 1 week of starting treatment.

The only other relevant factor was serial urinary cytology. Five of eight patients with measurable metastases, considered to have responded, showed conversion of urinary cytology from positive to negative, while none of 10 urine cytology positive non-responders showed cytology conversion on serial testing (Table 4). There was a suggestion that the responders whose cytology converted had a more durable response (3, 6, >6, 12, >12 months) than those whose cytology remained positive (2, 3, 4 months).

Table 3 Influence of Performance Status on Incidence and Duration of Response to Cytotoxic Chemotherapy

WHO/UICC performance status	*Number of cases*	*Complete response*	*Partial response*	*Median duration survival (months)*
0, 1, 2	63 (13)*	4 (3)*	17 (5)*	6 (6)*
3 and 4	15 (7)*	—	3 (1)*	1 (2)*

* Numbers in brackets relate to patients receiving methotrexate and cisplatin.

Discussion

Real progress in the treatment of chemosensitive tumours such as germ cell tumours, lymphomas and paediatric malignancies began to occur only when the incidence of complete response increased above 30%. Until recently, few studies of single agent or combination chemotherapy in bladder

Table 4 Changes in Urine Cytology in Patients with Invasive Bladder Cancer on Chemotherapy

Patient category	*No.*	*Positive to positive*	*Positive to negative*	*Negative to negative*
Measurable metastases				
Responders	11	3	5	4
Non-responders	12	10	—	2
Recurrent primary tumour				
Responders	8	4	1	3
Non-responders	12	11	—	1
Adjuvant methotrexate pre-radiotherapy	18	13	4	1

cancer patients reported a complete response and in those that did none reported histological evidence and none of the responses was durable.

The results from this small series of patients receiving methotrexate and cisplatin suggest that when taken in the context of either single agent or the other recently reported series from Edinburgh and the EORTC (Carmichael *et al.*, 1985; Stoter *et al.*, 1985), there was a definite increase in the incidence of complete response. Two other studies using methotrexate and cisplatin plus vinblastine (Harker *et al.*, 1983), or vinblastine plus adriamycin (Sternberg *et al.*, 1985) have reported complete responses of 30% and 38%. In the series reported by Sternberg *et al.* (1985), only 4 of 24 complete responders (9 of whom were established surgically) have relapsed with follow-up of more than 1 year. If this increased incidence of complete response can be confirmed by other centres, this will be the first time that a chemotherapy regimen has been developed which approaches the level of activity of radiotherapy and thus would justify its use as first-line treatment in patients with advanced tumours at presentation. A study to investigate this in patients presenting with T4 tumours is currently in progress under the auspices of the MRC. However, given the excessive toxicity of these new regimes, it would not be possible to consider them for use more extensively as first-line treatment until there was better substantiated evidence that the complete responses were durable.

Another point of interest from these data is that performance status need not necessarily be a bar to benefit from cytotoxic chemotherapy. In recent years there has been a trend to use poor performance status as a justification for exclusion of patients from clinical trials. Experience of chemotherapy in patients with germ cell tumours shows that improvement of performance status is often the first clinical sign that patients are benefiting from the chemotherapy. Patients with symptoms from their cancer made better by treatment are less likely to be disturbed by the side effects of chemotherapy than those with minimum symptoms. Since response did occur among the patients with poor performance status in this study, this exclusion is unjustified except as a method of improving the appearance of results. In the majority of patients who responded, especially in the methotrexate/cisplatin study, improvement of performance status was the first sign that the treatment was working.

An additional useful adjunct was urinary cytology, which suggests that those patients showing response by conversion from positive to negative cytology may have a more durable response. These results, together with those from Klein *et al.* (1983), suggest that serial monitoring of exfoliated tumour cells in urine may be an important way of providing early objective evidence of response to chemotherapy.

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The Authors

R. T. D. Oliver, MD, FRCP, Reader in Medical Oncology, The London and St Bartholomew's Hospital Medical Colleges, and Institute of Urology.
H. K. Kwok, FRCS, Registrar, Shaftesbury Hospital.
W. J. Highman, FRCPath, Consultant Cytologist, Institute of Urology and St Peter's Hospital.
J. H. Waxman, BSc, MRCP, Senior Registrar, The London and St Bartholomew's Hospital Medical Colleges, and Institute of Urology.

Requests for reprints to: R. T. D. Oliver, Department of Medical Oncology, The London Hospital, Whitechapel, London E1 1BB.

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The Value of Permixon in Benign Prostatic Hypertrophy

H. REECE SMITH, A. MEMON, C. J. SMART and K. DEWBURY

Departments of Urology and Radiology, Southampton General Hospital, Southampton

Summary—A double-blind trial comparing the effect of Permixon (160 mg bd) against placebo in the treatment of benign prostatic hypertrophy is described. In both groups a significant improvement in flow rate and subjective assessment of symptoms was seen. There was no significant difference between the results of treatment in either group.

Benign prostatic hypertrophy is an exceedingly common condition which affects most men over the age of 60. Although operative treatment is both effective and efficient, it requires considerable expertise and Health Service resources. A drug treatment for benign prostatic hypertrophy would, therefore, be of great value and we have tested the merits of Permixon, which is prepared from the fruits of *Serenoa repens*, a species of palm. The active material is comprised of fatty acids and their esters and has been found to have a significant antiandrogenic effect in the rat and the mouse (manufacturers' data).

Patients and Methods

The case notes of all patients on our urological waiting list which were labelled either "routine", "soon" or "urgent" were reviewed after discarding those notes which referred to patients who were thought to have malignant prostatic disease or whose symptoms did not fulfil the entry criteria. The remaining patients were invited to attend the hospital and the trial protocol was explained to them. Those who were willing to proceed were assessed by means of a full history, measurement of urinary flow rate, the taking of a mid-stream specimen of urine and assessment of residual volume by bladder echo-ography. A specimen of blood was also taken for routine laboratory screening tests. Patients who fulfilled the entry criteria listed in Table 1 were then invited to attend for a second visit, when they were given either Permixon or a placebo in a double-blind randomised manner, randomisation being carried out by allocating each patient a numbered folder. They were also given cards on which they could record the subjective assessment of their symptoms at the end of every week. After 2, 4, 8 and 12 weeks they returned to hospital and a repeat assessment was made of their symptoms (Table 1), their urinary flow rate and residual volume. At the same time they were questioned as to their tolerance of the drug. Measure-

Table 1 Symptoms

Scored by investigator	*Scored on self-assessment questionnaire*
Difficulty in micturition	Difficulty in passing urine
Impairment of urinary stream	Difficulty in starting urination
Urinary urgency	Urinary intermittency
Urinary hesitancy	Terminal dribbling
Urinary intermittency	Sensation of incomplete voiding
Terminal dribbling	Poor urinary stream
Sensation of incomplete voiding	Urinary urgency
Average daytime micturitions	Daytime frequency
Average nocturnal micturitions	Nocturnal frequency
Libido	Libido
Side effects	Side effects

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ment of symptoms by both observer and subject was on a three-point system: 0 = best, 1 = intermediate, 2 = worst.

Six months after completion of the trial, all patients were sent a postal questionnaire in which they were asked whether any improvement attained during the trial had been maintained over the succeeding 6 months.

Statistical analysis was carried out using paired '*t*' tests for changes from baseline values to final values. Between groups unpaired '*t*' tests (confirmed by Mann-Whitney U tests) were used. In all cases two-tailed statistical tests were applied.

Results

Eighty patients were included in the trial. Four patients, however, failed to attend for further follow-up and two withdrew after a few days because of "intolerable" side effects. Of the 74 patients for whom records were available, three were withdrawn because of acute urinary retention requiring surgery; one patient lost his pills and for a 3-week period took no medication. Seventy patients were, therefore, available for analysis, 33 of whom had taken Permixon and 37 of whom had taken placebo.

All patients were Caucasian. Table 2 shows the degree of matching for age, weight, nocturia, duration of symptoms and number of daytime micturitions.

Table 2 Comparison of Treatment Groups

	Permixon	*Placebo*	*Difference*
Age (years)			
Mean	66.15	67.03	t = 0.617
SD	5.86	6.03	NS
Range	55–77	55–80	
Weight (kg)			
Mean	74.13	73.39	t = 0.352
SD	5.25	10.47	NS
Range	64–85	52–105	
Duration of Symptoms (years)			
Mean	2.76	3.07	t = 0.981
SD	1.21	1.41	NS
Range	0.5–6.5	0.5–6.0	
Daytime micturition			
Mean	8.61	11.3	t = 1.701
SD	3.72	8.37	NS
Range	4.0–17.5	4.0–32.0	
Nocturia			
Mean	2.76	3.07	t = 0.981
SD	1.21	1.41	NS
Range	0.5–6.5	0.5–6.0	

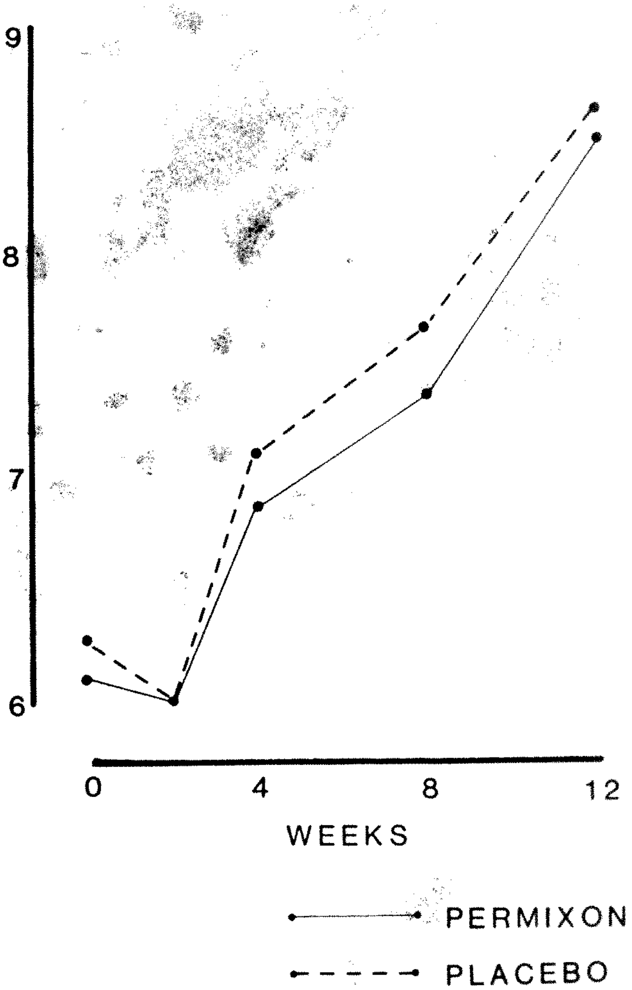

Fig. 1 Urine flow rate in ml/sec.

Investigators' Measurements

Urinary flow rate From Figure 1 it can be seen that in both treatment groups there was a similar and marked progressive improvement which reached statistical significance ($P < 0.01$) by the end of the trial. In both groups the increase from baseline by the end of the trial was approximately 35%. This improvement in urinary flow rate was seen in 60% of patients in both groups and differences between the groups were not significant.

Bladder residual volume There was no significant difference between the initial mean volumes in the two groups and in both groups there were erratic rises in residual volume during the course of the trial (Fig. 2). However, the changes in mean within the groups and the differences in mean between the groups failed to approach a statistically significant level.

Investigators' Assessments The results are shown in Table 3, where the pre-trial mean score is compared with the mean score for the similar symptom at 12 weeks. Separate columns show the Permixon and placebo values and these are compared in the final column. For many of the symptoms there was a significant improvement during the course of the trial. This improvement occurred in both groups and comparison between them revealed no significant difference for any single symptom. Statistical analysis was also carried out, comparing each assessment period against the pre-trial value. These data are not shown because the 12-week value in all cases gives a fair representation of the trend of the symptoms over the previous weeks.

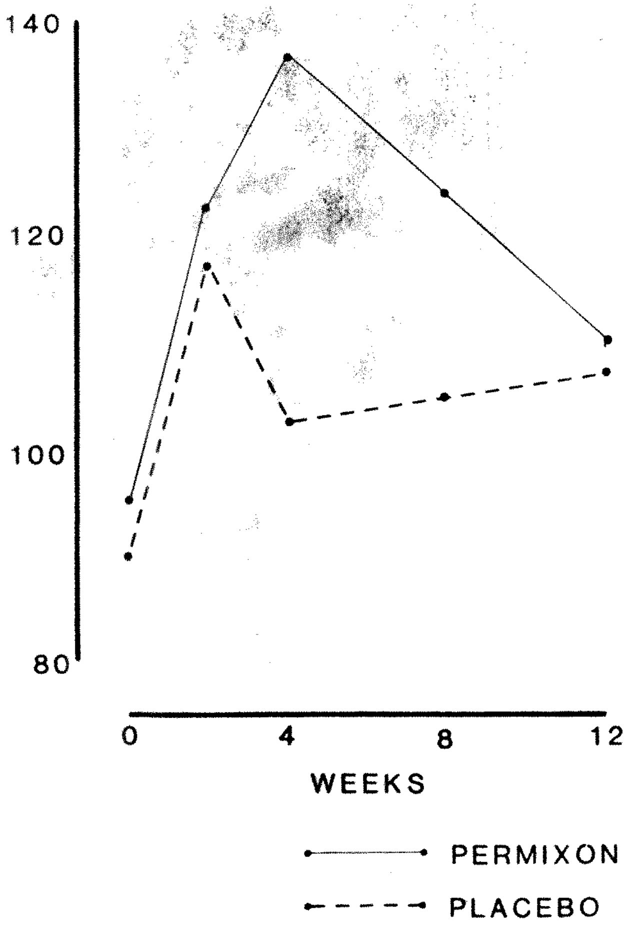

Fig. 2 Bladder volume in ml.

Six-month results All 70 patients replied and 26 reported an improvement. One felt he had relapsed since stopping the drug treatment. The others felt that improvement had been maintained and no surgery was required. In this group 12 had been taking Permixon and 13 Placebo.

Patients' self-assessment data The data from the patients' diary cards are shown in Table 4. The data for the pre-trial value are compared with the value expressed as the mean of the score at the end of the 12-week period. Although there were some significant improvements detected for individual symptoms over the course of the trial, the number of symptoms that were improved by placebo treatment was greater than the number of symptoms improved by Permixon treatment. Comparison between the two treatment groups for each symptom showed no significant improvement with either treatment (Table 3).

There are interesting differences between the scores obtained by the investigator and those given by the patients in their self-assessment data, but the number of daytime and nocturnal micturitions recorded by both methods is similar.

Libido Apart from one Permixon-treated patient who reported an increase in libido after 2 weeks' treatment, there were no other reports of altered libido in either group.

Side effects Two patients stopped Permixon treatment after 2 days and withdrew from the trial because of nausea and vomiting. One further patient stopped Permixon therapy for 2 or 3 days because of nausea and one patient stopped Permixon for 1 day because of dizziness. No other significant side effects were reported.

Laboratory investigations Only one patient showed a significant change in laboratory investigations during the course of the trial. This patient showed a marked rise in SGOT to a pathological level on completion of the trial. However, at this stage he was in hospital with an acute myocardial infarction. No other patient showed any individual changes in any of the laboratory variables measured.

Discussion

Benign prostatic hypertrophy is important in both economic and social terms since it affects a high proportion of the male population. Symptoms are unpleasant and in many cases socially unacceptable. Traditionally, the only definitive treatment

Table 3 Investigators' Assessments

	Permixon			*Placebo*			*Difference Permixon versus placebo*
Symptom	*Pre-trial*	*12 weeks*	*Difference*	*Pre-trial*	*12 weeks*	*Difference*	
Difficulty in micturition (mean)	1.39	0.67	$P<0.001$	1.14	0.63	$P<0.01$	NS
Impairment of stream	1.55	1.3	NS	1.72	1.14	$P<0.001$	NS
Urinary urgency	1.06	0.67	$P<0.01$	1.3	0.54	$P<0.001$	NS
Hesitancy	1.09	0.45	$P<0.001$	1.22	0.28	$P<0.001$	NS
Intermittency	0.72	0.58	NS	0.86	0.61	$P<0.005$	NS
Terminal dribbling	1.58	1.0	$P<0.001$	1.76	0.97	$P<0.001$	NS
Incomplete voiding	0.85	0.58	NS	1.05	0.56	$P<0.01$	NS
Average daytime micturitions	8.81	7.79	NS	9.41	8.88	NS	NS
Average nocturnal micturitions	2.89	1.86	$P<0.001$	2.95	1.9	$P<0.001$	NS

Mean scores for various symptoms. Pre-trial and 12-week scores are shown with statistical analysis for each symptom within groups and between groups.

Table 4 Patients' Self-Assessments

	Permixon			*Placebo*			*Difference between groups*
	Pre-trial	*Post-trial*	*Difference*	*Pre-trial*	*Post-trial*	*Difference*	
Difficulty in passing urine	0.88	0.7	NS	1.03	0.6	$P<0.05$	NS
Difficulty in starting urination	0.5	0.47	NS	0.6	0.32	$P<0.05$	NS
Intermittency	0.66	0.61	NS	0.91	0.40	$P<0.001$	NS
Terminal dribbling	1.13	0.8	NS	1.2	0.56	$P<0.001$	NS
Sensation of incomplete voiding	0.84	0.44	$P<0.05$	0.91	0.63	$P<0.05$	NS
Poor stream	1.69	1.20	$P<0.01$	1.66	1.32	$P<0.05$	NS
Urgency	1.38	1.0	$P<0.01$	1.14	0.72	NS	NS
Average daytime micturitions	8.31	8.60	NS	10.35	9.06	NS	NS
Average nocturnal micturitions	2.44	2.04	NS	2.45	1.8	$P<0.05$	NS

Mean scores for various symptoms with statistical analysis within groups and between groups.

available is surgery and this results in great pressure on resources within the Health Service and, in many cases, long waiting lists. An effective medication to ameliorate the symptoms of benign prostatic hypertrophy would be of immense value.

Phenoxybenzamine has been the most widely tested drug, with some authors (Whitfield *et al.*, 1975; Caine *et al.*, 1978) reporting a beneficial effect, whilst others (Brooks *et al.*, 1983) have found it to be ineffective. Other α blocking drugs such as prazosin (Hedland *et al.*, 1983) have been used, as has probucol (Resnick *et al.*, 1983) and many other drugs such as tamoxifen, candicidin and luteinising hormone antagonists. Such disparate results have been obtained in the drug treatment of benign prostatic hypertrophy that the value of drugs in this condition is open to dispute.

The most remarkable feature of the results obtained during this trial is a demonstration that dramatic improvements, even in such quantifiable variables as urinary flow rate, can result from placebo treatment, although similar results have been shown by other authors (Hedland *et al.*, 1983; Resnick *et al.*, 1983). However, it is clear that the results obtained offer no support to the suggestion that Permixon is of benefit in prostatic hypertrophy.

In conclusion, whilst the regime of Permixon used in this trial was safe, well tolerated and associated with considerable symptomatic improvement, we have no evidence that this improvement was due to anything more than the psychosocial value of being involved in the trial and meeting a number of sufferers from a similar condition. In particular, a significant proportion of patients came to a greater understanding of their disease and no longer required surgical treatment. Thus it may be that if more time were spent counselling patients with symptoms of benign prostatic hypertrophy, the operative workload could be reduced. A further trial would be required to determine whether simple counselling would be as effective as this double-blind randomised controlled trial of a new therapy.

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The Authors

H. Reece-Smith, MS, FRCS, Consultant Surgeon, Battle Hospital, Reading.

A. Memon, MB,BS, Registrar in Surgery, Southampton General Hospital.

C. J. Smart, FRCS, Consultant Urologist, Southampton General Hospital.

K. Dewbury, FRCR, Consultant Radiologist, Southampton General Hospital.

Requests for reprints to: C. J. Smart, Department of Urology, Southampton General Hospital, Tremona Road, Southampton.

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Evaluation of Biopsy Techniques for Androgen Receptor Assay in Human Prostatic Tissue

NATASHA KYPRIANOU, H. WILLIAMS, W. B. PEELING, P. DAVIES and K. GRIFFITHS

Tenovus Institute for Cancer Research, University of Wales College of Medicine, Cardiff, and Department of Urology, St Woolos Hospital, Newport

Summary—Androgen receptors were assayed in nuclei prepared from human benign hypertrophic prostate tissue obtained at retropubic prostatectomy by transurethral resection (TURP) and by cold punch resection. Androgen receptor was not detected in 70% of the transurethrally resected samples, and in those cases where receptors were observed they showed no correlation with enucleated samples. However, androgen receptors were detected in all cold punch resected samples and enucleated tissue with similar concentrations evident in samples from the same gland. These results suggest that prostate specimens collected by TURP are not suitable for androgen receptor analysis, whereas the technique of cold punch resection yields prostate samples that are more reliable for a correct evaluation of androgen receptor content.

Androgen receptors have a central, fundamental part to play in the function of the prostate and consequently have become the focus of much interest and research, particularly in their relation to benign hyperplasia and carcinoma of the prostate. It is well recognised that assay of androgen receptors is a precise, highly skilled procedure that has many technical problems and difficulties (Davies, 1978), but great attention must also be paid to the conditions of sampling human prostatic tissue for receptor studies because the most valid end results must come from tissue that has been least damaged by the biopsy procedure. Transurethral resection of prostatic tissue would seem to be the easiest method by which urologists could acquire substantial amounts of material for receptor studies but the arc generated by the cutting loop of resectoscopes could seriously influence results of assay techniques because androgen receptors are unstable at high temperatures and so could be affected by transfer of heat into the interior of resected chippings. This situation has been examined by some workers, some of whom consider that it is a handicap but not an objection to receptor assay using resector tissue, particularly when chippings are sufficiently large to permit removal of external charring (Snochowski *et al.*, 1977; Bashirelahi *et al.*, 1980; Ghanadian and Auf, 1980; Nozumi *et al.*, 1981). The frequency of current used for resection can also influence results of receptor assays (Albert *et al.*, 1982). The alternative technique for removal of prostatic tissue endoscopically is cold punch resection, which is unlikely to expose the interior of resected chippings to any physical trauma.

This study was undertaken to compare androgen receptors in prostatic tissue removed by cold punch resection with tissue taken by electroresection, and to evaluate the relative merits of two techniques for measurement of androgen receptors in prostatic tissue. Nuclear receptor levels were studied because of recent observations that cytoplasmic receptor may be an artefact (King and Greene, 1984; Welshons *et al.*, 1984) and increasing evidence that androgen receptors are localised predominantly in nuclei of human prostatic tissue (Menon *et al.*, 1978; Hicks and Walsh, 1979; Trachtenberg and Walsh, 1982).

Patients and Methods

Twenty patients with clinically suspected benign

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prostatic hyperplasia (BPH), whose prostatic mass exceeded 70 g measured by ultrasonography *per rectum*, underwent retropubic prostatectomy. All had preliminary cysto-urethroscopy to exclude unexpected bladder, prostatic or urethral pathology, and none was found in any of the patients. Histologically, BPH was proven in all patients.

Following preliminary cysto-urethroscopy, several samples of tissue were removed from the right lobe of the prostate using a 27F cold punch resectoscope. Following this, from areas adjacent to those which had been removed by cold punch, several more samples of prostatic tissue were removed transurethrally using a 24F or 27F resectoscope. After haemostasis of the area of biopsy with diathermy, the patient was repositioned on the operating table and a standard retropubic prostatectomy was performed. From the enucleated operative specimens two further samples were taken (a) from the right lobe of the prostate, selecting tissue adjacent to the area where TURP and cold punch specimens had been taken, and (b) from the left lobe, which had not been subjected to endoscopic removal of tissue or to diathermy. All prostate samples were immediately transported on crushed ice for analysis or else rapidly processed for storage at −170°C for later study.

Nuclear androgen receptor assay

Nuclei were purified from all samples of human prostate tissue as described previously (Davies and Griffiths, 1976) and their purity was assessed by phase-contrast light microscopy. Recoveries of homogenate DNA (%) as purified nuclei were as follows (± S.D., n = 20 in each case), TUR, 50 ± 5.2 cold punch, 59 ± 4.1; right and left lobe removed at retropubic prostatectomy respectively, 58 ± 5.8 (n = 11) and 56 ± 4.9 (n = 10). In all cases DNA was determined according to the method of Burton (1956).

Concentrations of androgen receptors in prostate nuclei were estimated using 5α-dihydro [1,2,4,5,6,7-^{3}H] testosterone ([^{3}H]DHT; 140-150 Ci/mmol; Amersham International PLC, Bucks, UK) by the method of Davies *et al.* (1977) involving precipitation of receptor-steroid complex, with protamine sulphate, subsequent to incubation and exchange of endogenous steroid with radioactive ligand.

Kinetic appraisal of all ligand-retention was achieved using a non-linear least squares model based on a mass action model (Feldman, 1972).

Results

Nuclear androgen receptor levels and binding parameters as determined by the conventional exchange assay methodology using [^{3}H]DHT as labelled ligand are summarised in the Table. Of the 20 TUR samples analysed from BPH patients, only six contained detectable nuclear androgen receptors and at a significantly lower concentration than those estimated for prostate samples removed from the same patient by cold punch resection or enucleation. These TUR specimens were the largest obtained, the approximate weight of each prostatic chip being 500 to 800 mg, and showed minimal charring which was easily removed from the tissue before it was processed.

Nuclear androgen receptors, however, were detectable in all cold punch resected and enucleated tissue with similar concentrations of receptor evident in samples from the same gland. Comparison of the receptor levels estimated for samples of the left lobe and the remainder of the right lobe removed at open prostatectomy yielded a correlation coefficient of 0.94 (n = 10). Comparison between cold punch resected specimens and the remainder of the right lobe gave a correlation coefficient of 0.87 (n = 10). Finally, comparisons between androgen receptor levels estimated in cold punch samples and those of the left lobe yielded a correlation coefficient of 0.84 (n = 10). This could be considered a relatively good correlation among cold punch resection and enucleated tissue in view of the generally accepted assumption that all nuclei in a given prostate specimen have the same binding capacity. Androgen receptor quantitation in nuclei prepared from large tissue samples (such as the retropubic prostatectomy specimens) would be less influenced by the heterogeneous distribution of receptor molecules. Therefore the estimates of nuclear androgen receptor of cold punch specimens correlated well with matched evaluations of bulk tissue obtained by open prostatectomy. Cold punch resection, therefore, seems to be far superior to TURP for sampling of prostatic tissue as it allows a fair reflection of androgen receptor content.

Saturation analysis of [^{3}H]-DHT binding in nuclei prepared from the enucleated part of the right lobe of the prostate and Scatchard analysis of the saturable binding obtained for a cold punch resected specimen from the same patient yielded very similar receptor concentrations and binding affinities ([AR] = 1117 fmol/mg DNA, Kd = 10.4 nm; [AR] = 1380 fmol/mg DNA, Kd = 10.4 nM respec-

Table Androgen Receptor Content ([AR] fmol/mg DNA where Undetectable Signified by "0", when not done Signified by Blank Column and Binding Affinity (Kd, nmol/l) of Nuclei Prepared from Specimens of BPH Prostate Tissue Obtained by Transurethral Resection (TUR), Cold Punch Resection (CP) and at Retropubic Prostatectomy (RPP: "Right" and "Left" Refer to Separate Lobes).

Patients						*RPP*			
Initials	*Age (years)*	*TUR*		*CP*		*Right*		*Left*	
		[AR]	Kd	[AR]	Kd	[AR]	Kd	[AR]	Kd
(A.H)	74	0		1190	14.1	911	5.0	915	3.8
(R.M.)	72	0		836[a]	7.5	968	7.6	1000	6.9
(L.H.)	72	0		1010	3.1	1040	9.4	807	2.8
(W.G.)	59	0		576[b]	4.8	458[b]	4.7	598[b]	3.7
(C.D.)	87	0		1320	9.3	1073	10.4	969	7.9
(H.B.)	78	0		1850	19.3	1491	4.4	1584	11.2
(I.W.)	61	648[c]	8.0	1180	3.5				
(L.B.)	72	359[c]	2.4	903	3.2	1116	9.3	1200	15.4
(A.C.)	70	0		2100	6.6				
(G.E.)	67	391[b,c]	12.1	561[b]	7.4	487[b]	14.5	496[b]	9.4
(J.T.)	58	436[c]	5.5	745	4.3				
(A.T.)	84	0		1010	2.3				
(R.R.)	59	299[c]	4.8	767	5.6	832	9.1	937	4.9
(R.H.)	67	0		374[b]	6.2				
(F.V.)	68	380[c]	10.4	898	6.1				
(F.G.)	77	0		514[a]	6.7				
(W.N.)	74	77[c]	1.7	969	4.7				
(J.A.)	61	0		561	12.7				
(A.L.)	76	0		813	12.2	697	1.1	796	13.4
(D.S.)	55	0		1030	5.7	708	6.0		

[a] Insufficient amount of tissue available for complete saturation analysis of [^{3}H]-DHT binding to nuclear androgen receptor.

[b] Prostate samples were stored under liq. N_2 (−170°C) for 3 to 4 weeks before assayed.

[c] TUR specimens were obtained with 27F resectoscope loop and were relatively larger (500-800 mg) and comparatively free of charring.

tively). However, it was not possible to analyse binding data obtained for the TURP specimen removed from the same patient. Saturation of binding could not be demonstrated due, most probably, to heat denaturation of receptor protein during the surgical removal of tissue, leaving only non-specific binding. Even in those cases in which binding data obtained for a TUR specimen could be analysed, specific binding was significantly lower than that observed in the corresponding cold punch and retropubic prostatectomy samples.

Discussion

The data presented in this study indicate clearly that the method of sampling of prostatic tissue from patients significantly affected the results of androgen receptor quantitation. Specimens of BPH removed by TURP were not suitable for androgen receptor analysis, for only 6 of the 20 TURP samples analysed contained detectable amounts of androgen receptors. These particular TURP chippings were the largest obtained (500-800 mg) and were relatively free of charring. This is, of course, to be expected.

In this study we were able to detect nuclear androgen receptors in all prostate samples obtained by cold punch resection and in 75% of the cases the androgen receptor levels correlated well with those measured in enucleated tissue removed by retropubic prostatectomy from the same patient. It would be premature to claim significant correlations among receptor levels determined in specimens obtained by different sampling techniques. Absolute correlations are limited by the assumption that all nuclei have equivalent binding capacity without considering the relative contributions from different cellular types. Whereas such considerations of gross receptor heterogeneity could account for variations among enucleated right lobe or left lobe and cold punch samples concerning quantities of nuclear androgen receptors, they could not account for the aberrations of detection observed in TURP specimens. While the dissociation constants (K_d) determined for the human prostatic nuclei in this study (range 1.1-19.3 nM) and the values found in the literature (Trachtenberg *et al.*, 1981) (range 1.2-4.8 nM) are both in nanomolar range, they do differ in absolute terms. This apparent discrepancy is probably due either to imprecision of Scatchard analysis when applied to small amounts of prostate tissue or to the effects of the non-ionic detergent Triton-X-100, which was used for partial purification of nuclei and which has been observed to raise the K_d for the binding of 5 α-DHT to prostatic nuclei (Kline *et al.*, 1981).

In conclusion, this comparative study suggests that cold punch resection yields prostate specimens which are more reliable for the assay of the presence as well as the quantity of androgen receptors than TURP specimens.

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The Authors

Natasha Kyprianou, MSc, Research Assistant, Tenovus Institute for Cancer Research.

H. Williams, MB, Senior House Officer, Department of Urology, St Woolos Hospital.

W. B. Peeling, FRCS, Consultant Urologist, Department of Urology, St Woolos Hospital.

P. Davies, MSc, PhD, Senior Research Associate, Tenovus Institute for Cancer Research.

K. Griffiths, PhD, DSc, Director of Research, Tenovus Institute for Cancer Research.

Requests for reprints to: Natasha Kyprianou, Tenovus Institute for Cancer Research, University of Wales College of Medicine, The Heath, Cardiff CF4 4XX.

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Objective Responses to Ketoconazole Therapy in Patients with Relapsed Progressive Prostatic Cancer

GORDON WILLIAMS, D. J. KERLE, H. WARE, A. DOBLE, HELEN DUNLOP, C. SMITH, JANET ALLEN, T. YEO and S. R. BLOOM

Departments of Surgery and Medicine, Hammersmith Hospital and Royal Postgraduate Medical School, London

Summary—The contribution of adrenal androgens to the maintenance and progression of so-called hormone-unresponsive prostatic carcinoma was studied in 20 patients with advanced relapsed disease. The role played by testicular androgens had been negated by prior orchiectomy or concurrent LHRH analogue therapy. Ketoconazole, an antifungal agent which inhibits adrenal and testicular androgenesis, administered in a dose of 400 mg 8-hourly, resulted in optimal suppression of adrenal androgens. The mean serum androstenedione concentration fell from 8.01 ± 0.84 nMol/l to 1.55 ± 0.25 nMol/l, $P < 0.001$, and serum testosterone from 1.25 ± 0.14 nMol/l to 0.36 ± 0.06 nMol/l, $P < 0.01$, after 6 months treatment. There was, however, no significant difference between patients receiving 400 and those receiving 200 mg. Androgen suppression resulted in six objective and ten subjective clinical responses. Ablation of both testicular and adrenal androgens can now be achieved using ketoconazole in combination with orchiectomy or LHRH analogues, but the high incidence of side effects may preclude its use in all patients with prostatic cancer. The results of this study support the concept of "total androgen ablation" as primary therapy in advanced prostatic cancer as a possible means of improving survival in this common malignancy.

Endocrine treatment of advanced prostatic cancer has been aimed at suppressing the major source of circulating testosterone from the testes and is achieved by either oestrogen administration, which inhibits pituitary secretion of gonadotrophins, or orchiectomy. Initial clinical response rates of 70 to 80% following either form of therapy have been reported (Resnick and Grayhack, 1975; Whitehead, 1981). However, most of these patients will relapse in 2 to 3 years of commencing endocrine therapy, and once relapse occurs 50% will die within 6 months. These therapies do not suppress adrenal androgens, which may increase after orchiectomy and encourage continued tumour growth (Sciarra *et al.*, 1973). Attempts to inhibit adrenal androgen production using pituitary ablation, adrenalectomy (Murphy *et al.*, 1971) or aminoglutethimide (Sanford *et al.*, 1976; Worgul *et al.*, 1983) have been made in patients who have failed conventional endocrine treatment. These latter therapies all have considerable disadvantages and when instituted for end-stage relapsed disease, objective response rates are poor and of short duration (Sanford *et al.*, 1976; Fitzpatrick *et al.*, 1980; Worgul *et al.*, 1983). The use of these forms of therapy as a component of primary endocrine treatment has not been attempted because of the high incidence of serious side effects. Steroid supplements, which are obligatory following pituitary ablation or aminoglutethimide therapy, may be responsible in part for the adrenal suppression achieved.

Ketoconazole, an imidazole antifungal agent, has been shown to inhibit both testicular and adrenal androgenesis (Pont *et al.*, 1982a and b). Objective responses following ketoconazole administration in patients with newly diagnosed prostatic cancer have been reported (Trachtenburg and

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Pont, 1984), but serum testosterone did not reach castrate levels in all patients and its short duration of action necessitates a strict 8-hourly dose regime. We have previously reported two patients with relapsed progressive disease treated with ketoconazole who have shown an improvement in objective response measurements (Allen *et al.*, 1983). We now present our experience of ketoconazole administration in a further 20 patients.

Patients and Methods

Informed consent was obtained prior to treatment from 20 patients aged 55 to 77 years (mean 68.5) with histologically confirmed prostatic carcinoma who had relapsed following single or multiple sequential endocrine therapy (Table 1). Each patient underwent the following staging procedures: digital rectal examination, tartrate labile acid phosphatase, alkaline phosphatase, intravenous urography, technetium labelled bone scanning with appropriate radiographs, and in one patient a sagittal section nuclear magnetic resonance scan before and 6 months after treatment. All objective response measurements were documented at regular intervals throughout the study, using the British Prostate Group Criteria.

Table 1 Previous Hormonal Therapies

Previous hormonal treatment	*No. of patients*	*Time from initial diagnosis to introduction of ketoconazole (months)*
LHRH	4	8.5
Oestrogen + orchiectomy	2	24
Oestrogen + LHRH	5	23
Orchiectomy + LHRH	6	29
Orchiectomy + oestrogen + LHRH	2	43
Orchiectomy + cyproterone acetate + LHRH	1	60

Subjective criteria were recorded before treatment and at each subsequent visit using a scoring system for activity, pain and analgesia (Oken *et al.*, 1982). Blood for measurement of serum testosterone and dihydrotestosterone (Ghanadian *et al.*, 1975), androstenedione (Ghanadian and Puah, 1983), cortisol by "Gamma Coat" kit (Clinical Assays, Cambridge, USA), ACTH (Rees *et al.*, 1971) and LH (Marshall *et al.*, 1973) were taken before treatment, at 5 days, 2 weeks, 1 month and monthly thereafter. All samples for endocrine assessment were collected between 9 and 10 a.m. On the first treatment day 4- and 8-h samples were taken to measure the acute response of androstenedione to a single dose of ketoconazole. The diurnal rhythm of serum cortisol and ACTH was studied in all patients after 6 months of ketoconazole therapy.

Those patients who had not received a prior orchiectomy and were taking the LHRH analogue ICI 118630, 250 µg daily, were continued on this therapy.

Ketoconazole was administered to 15 patients at a dose of 400 mg 8-hourly (high dose) but was reduced to 200 mg 8-hourly (low dose) in 6 patients because of anorexia and nausea, after a mean interval of 30 days (range 5-70). The remaining five patients started on 200 mg tds. A satisfactory clinical response has been reported at this lower dose (Trachtenburg *et al.*, 1983). Endocrine data were analysed in accordance with the dose of ketoconazole being administered at the time of each follow-up visit and were expressed as mean ± SEM. Significance was determined using paired and unpaired Students *t* tests.

Results

Clinical

Eight patients died of progressive metastatic disease within 14 weeks of commencing treatment (mean 7.5 weeks, range 4-14) (Fig. 1). Six of these patients were on low dose and two on high dose regimes.

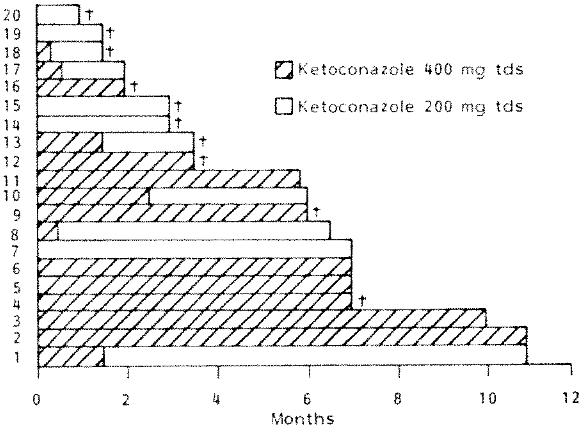

Fig. 1 Clinical outcome in 20 patients with advanced relapsed prostatic cancer following two dose regimes of ketoconazole.

Eleven patients have survived for more than 14 weeks. Four maintained on low dose therapy are alive for a mean period of 8 months. Partial objective response was documented in one patient and

Table 2 Changes in Objective Response Measurements and Resulting Clinical Response (British Prostate Group) in 11 Patients Following 6 Months of Ketoconazole Therapy

Patient	*Dose*	*T stage*	*Acid phos. (iu/l)*	*Bone scans*	*Clinical response*
2	1200 mg/day	T0→T0	28→25	Stable	Stable
3	,, ,,	T4→T4	20→6	Stable	Partial
4	,, ,,	T1→T0	125→322	Improved	Partial
5	,, ,,	T0→T0	2.9→N	Stable	Partial
6	,, ,,	T4→T4	6→N	Improved	Partial
9	,, ,,	T3→T4	6→N	Worse	Progression
11	,, ,,	T0→T0	9→N	Complete resolution	Complete
1	600 mg/day	T3→T0	68→69	Stable	Stable
7	,, ,,	T0→T0	5.4→N	Worse	Progression
8	,, ,,	T4→T4	1.8→2.1	Worse	Progression
10	,, ,,	T4→T4	241→6.5	Resolution some lesions	Partial

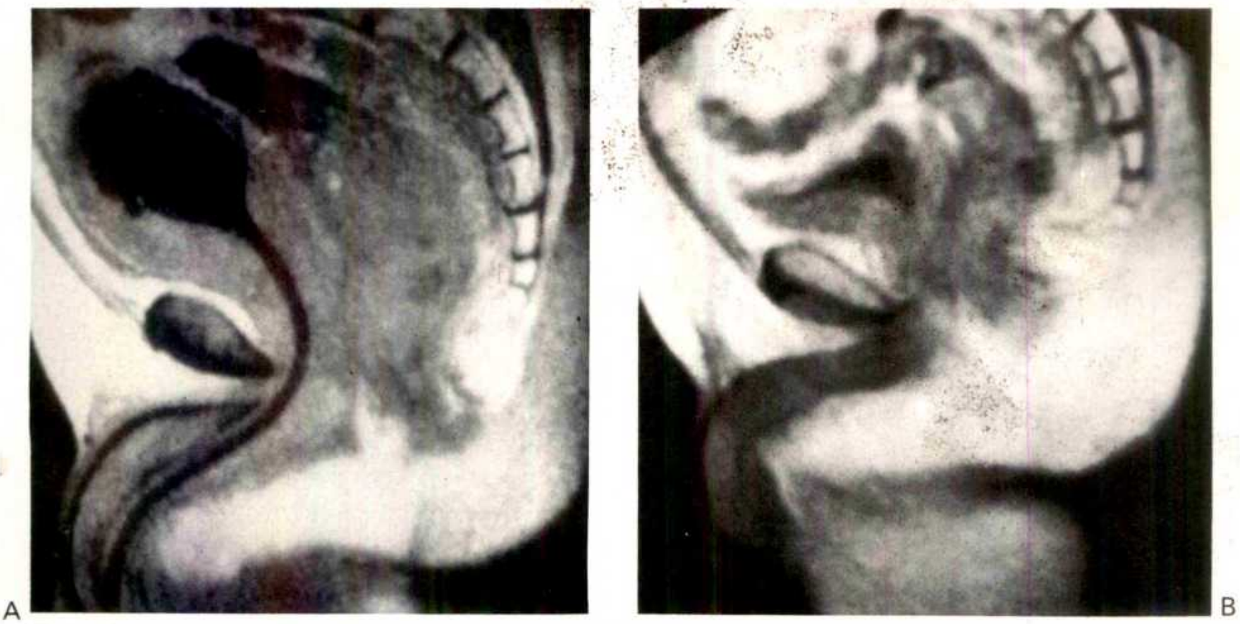

Fig. 2 Sagittal section nuclear magnetic resonance (NMR) scans (A) before and (B) after 6 months ketoconazole 400 mg tds. Prostatic tumour volume has halved and the previously stenosed bowel lumen is clearly visible.

another has stable disease, but the other two have shown evidence of disease progression manifest by worsening bone scans. Seven patients have been on high dose therapy throughout and have shown evidence of response (Table 2). The likelihood of a response to ketoconazole did not appear to relate to any previous combination of therapies.

Objective Response

1. *Local disease*

The volume of prostatic tumour halved and unilateral upper tract obstruction resolved in Patient 3, whose disease was assessed by nuclear magnetic resonance scanning (Figs. 2A and B) and serial ultrasonography. Digital assessment in the remaining patients showed a prostate tumour volume reduction of at least 50% in two patients (4 and 6). Downstaging of the prostatic tumour occurred in one of these. No change in the state of local disease was detected in the remaining four patients.

2. *Prostatic Acid Phosphatase*

The tartrate labile acid phosphatase was elevated in 11 of 12 patients who commenced and continued on high dose therapy for at least 1 month. Values fell by more than 50% in seven of these within this first month of treatment and have reached the nor-

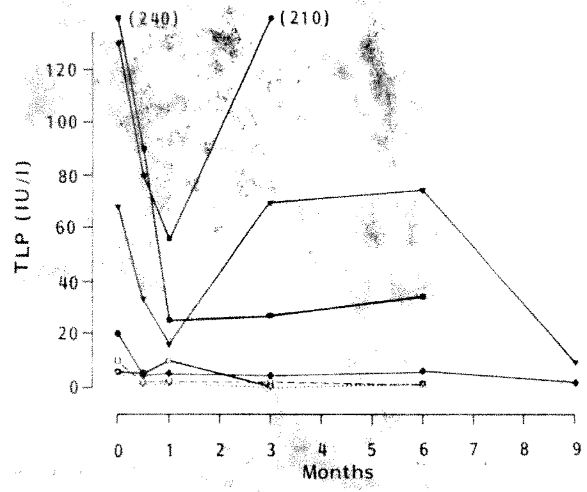

Fig. 3 The tartrate labile acid phosphatase fell by more than 50% in seven patients following ketoconazole 400 mg tds. This initial fall is maintained in six patients and three have normal values after 6 months' treatment.

Table 3 Changes in the Subjective Scores After Ketoconazole. Significant Responses are Indicated by an Improvement of Two or More Points (Rees *et al.*, 1971)

		Subjective score: points improvement			
Time	*Dose*	*<2*	*2*	*3*	*4 or more*
One month	High	5			6
	Low	6	1	1	
Three months	High	6	2		
	Low	7			
Six months	High	7			
	Low	2	1		

mal range in three of eight patients treated with high dose therapy for 3 months (Fig. 3).

3. *Bone Scans*

Seven patients who had been on high dose therapy for 6 months had a further bone scan. Three scans have improved, with resolution of lesions confirmed radiographically, and three remain stable. Patient 4 had an improvement in both local tumour and bone scan but also a steady rise in acid phosphatase; the bone scan showed no new lesions, improvement of existing lesions and resolution of some. These changes in objective response parameters are summarised in Table 2.

Subjective Response

The changes in the subjective scores are shown in Table 3. The maximum benefit was seen in the first month's treatment.

Endocrine Response

A prompt fall in the mean serum androstenedione concentration was seen within 8 h of commencing therapy and was most marked in patients on high dose (Fig. 4A). The continuing fall in both groups is shown in Figure 4B. All patients had castrate levels of serum testosterone before treatment. Further falls in the mean serum concentrations of testosterone are shown in Figure 5.

The mean serum concentration of dihydrotestosterone fell from 0.85 ± 0.07 nMol/l to 0.47 ± 0.12 nMol/l (n = 6, $P > 0.1$) after 6 months' high dose treatment and to 0.64 ± 0.06 nMol/l (n = 6, $P > 0.3$) after 3 months of low dose therapy.

Serum cortisol remained within the normal range (200-700 nMol/l) during the course of study in all patients. The mean serum concentration changed from 747 ± 77 nMol/l (n = 17) to 548 ± 80 nMol/l (n = 6, $P > 0.05$) after 6 months of high dose ketoconazole treatment. Low dose resulted in a fall to 544.5 nMol/l in two patients after 6 months.

The serum ACTH was in the normal range (10-80 ng/l) in 12 of 14 patients studied prior to treatment. Six of these patients (five high dose and one low dose) showed elevation of serum ACTH (range 88-311 ng/l) within 3 days of commencing treatment. There was a progressive rise in four of these patients alive after 3 months' treatment. Of the two patients alive at 6 months, the serum ACTH has returned to normal in one. The six patients with no rise in ACTH at the beginning of treatment remained normal throughout the period of study. Five further patients had ACTH estimations for the first time after 6 months' treatment and four (two high and two low dose) were elevated (range 89-260 ng/l).

The diurnal variation of serum cortisol and ACTH was studied in seven patients (four high and three low dose) between 6 and 12 months of ketoconazole therapy. The 8 a.m. serum cortisol was normal in all patients but at midnight four patients (two high and two low dose) had elevated levels (range 260-450 nmol/l; normal range < 250 nmol/l).

Correspondingly, four patients (three high and one low dose) had elevated serum ACTH concentrations at 8 a.m. (range 154-260 ng/l) and three were normal. At midnight all ACTH values were elevated (range 27-94 ng/l; normal range < 10 ng/l).

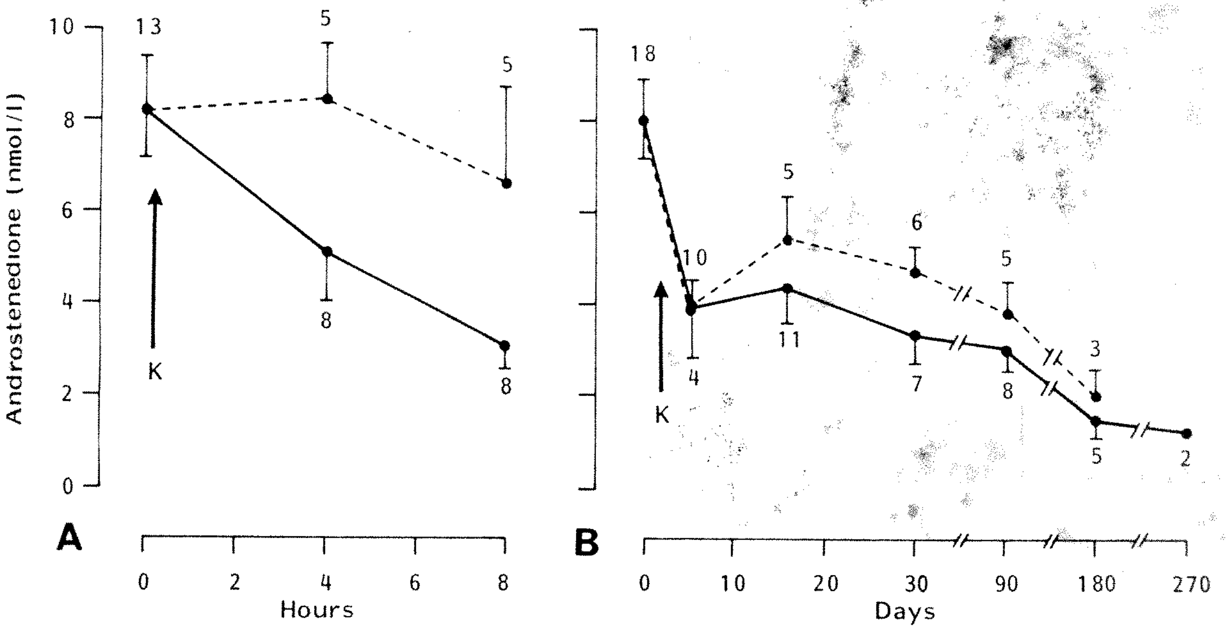

Fig. 4 Mean serum androstenedione concentrations following institution of ketoconazole therapy (K) 400 mg tds ——— and 200 mg tds – – –. (A) Suppression is seen after 8 h of single dose of 200 mg ($P = 0.04$) and 400 mg of ketoconazole ($P = 0.005$). (B) A significant difference between the two dose regimes after 8 h ($P < 0.001$) is not maintained during long-term follow-up.

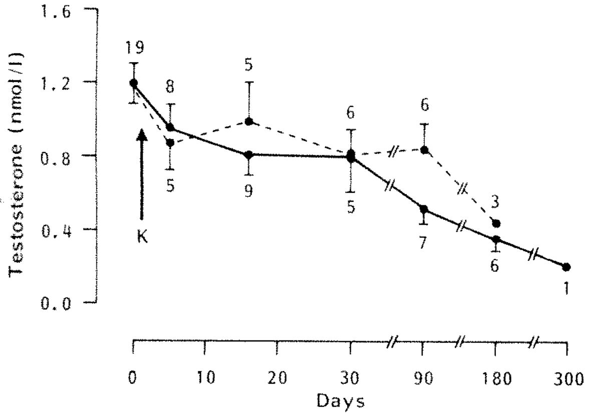

Fig. 5 Mean serum testosterone following institution of ketoconazole therapy (K) 400 mg tds ——— and – – – 200 mg tds. A significant fall below castrate concentrations is seen following 180 days of high dose therapy ($P < 0.01$).

Side Effects

Eleven of the 20 patients complained of nausea and anorexia immediately after institution of ketoconazole therapy (8 high dose and 3 low dose). Dosage was reduced to 200 mg 8-hourly in six of the eight high dose patients but nausea persisted in four, requiring withdrawal of the drug in one. A persistent but acceptable level of nausea was tolerated by six high dose and three low dose patients throughout the treatment period.

Six high dose patients showed a transient rise in the serum aspartate transaminase (range 51-77 iu/l; normal range 21-40) which occurred between 5 days and 2 months following the start of ketoconazole. In only one patient was this associated with elevation of serum bilirubin to 22 µmol/l (normal range 4-17) after 1 month of therapy. The serum bilirubin rose transiently in two further patients, one high dose and one low dose, to 18 µmol/l after 2 months and 21 µmol/l after 3 months' treatment respectively but returned to normal without drug withdrawal. None of the patients who have been on therapy for more than six months has any abnormality of liver function.

Hypocalcaemia developed in two patients, one high dose and one low dose. The serum calcium fell to 1.87 nmol/l after 5 days' treatment in the high dose patient (normal range 2.15-2.65) and remained low during 4 months of ketoconazole treatment. The low dose patient was hypocalcaemic prior to ketoconazole treatment but fell further to 1.65 nmol/l after introduction of the drug.

Discussion

Between 60 and 80% of patients with prostatic cancer respond to endocrine therapy aimed at lowering serum testosterone. Because of this success in the palliation of symptoms there has been little deviation from conventional treatment using oestrogens or orchiectomy as primary therapy.

However, after 2 to 3 years' treatment the majority of patients will relapse and this is thought to indicate the development of tumour cells growing independently of their hormone environment. It is not surprising that further clinical responses are rarely seen following additional hormonal manipulation directed solely at the pituitary gonadal axis (Stone *et al.*, 1980; Allen *et al.*, 1984).

Man is unique in having adrenals which secrete large quantities of pre-cursor steroids which are converted into potent androgens. The adrenal output accounts for up to 10% of androgen production and remains unaffected by conventional endocrine therapy with oestrogens or orchiectomy. Furthermore, following such therapy intraprostatic concentration of dihydrotestosterone, the most active androgen within the prostate, remains as high as 50% of levels found in intact patients (Geller *et al.*, 1979). High doses of ketoconazole, a widely used drug for the treatment of fungal diseases, blocks the synthesis of testosterone in both the testes and the adrenals at a cytochrome P450 dependent step, *i.e.* where 17 alpha, 20 alpha dihydroxy-progesterone is transformed into androstenedione.

This inhibition of adrenal androgen production by ketoconazole has allowed us to evaluate the role of these androgens in patients with advanced relapsed prostatic cancer—tumours thought to be hormone-independent. Recent refinements in radioimmunoassay techniques for androgen assay and the acceptance of standard response criteria in prostate cancer have enabled us to correlate adrenal androgen suppression with clinical response.

The patients treated all had severe disease, eight dying from their malignancy within 14 weeks. Subjective improvement was seen in 10 patients within the first 3 months of treatment, though the majority of these were in the first month. One patient on high dose ketoconazole, who had been confined to bed with severe perineal pain, was able to mobilise to near-normal activity and withdraw from narcotic analgesia. This degree of improvement was unlikely to be due to a placebo effect. Of the 11 patients alive at 6 months and assessed by the British Prostate Group criteria of response (Chisholm and Beynon, 1983), one complete and five partial responses were seen. The objective responses of some patients were dramatic, in particular the relief of almost total rectal occlusion by a massive encircling tumour (Fig 2A and B), and a complete resolution of secondaries confirmed by bone scan in another.

This study has shown that ketoconazole markedly inhibits production of androstenedione at both dose regimes and produces further significant falls in the already castrate levels of testosterone and dihydrotestosterone; although not measured in this study, an elevation of progestogens could be expected.

These results strongly suggest that adrenal androgens play a significant role in the maintenance of some so-called hormone-unresponsive prostatic tumours and provide further evidence for the concept of total androgen ablation (*International Journal of Andrology*, 1984) for the primary treatment of prostatic cancer.

Alterations in serum cortisol occurred at some stage in most patients during the course of treatment. However, no patient had levels below the normal range and cortisol supplements were not required. Maintenance of a cortisol within the normal range has been achieved by elevation of ACTH in most patients. Medical adrenalectomy achieved with aminoglutethimide (Sanford *et al.*, 1976; Fitzpatrick *et al.*, 1980) invariably requires cortisol replacement and this may, in part, account for the clinical effects seen.

Aminoglutethimide, an alternative means of producing a medical adrenalectomy, is not without side effects, nor is ketoconazole. Six patients were unable to tolerate high dose therapy because of persistent nausea, although this does not appear to be a problem when ketoconazole syrup is used rather than ketoconazole tablets. Ketoconazole is also hepatotoxic in some patients (Heiberg and Svejgaard, 1981; Lewis *et al.*, 1984) and has recently been the subject of a warning by the Committee on Safety of Medicines. The incidence of liver disease is approximately 1 in 15,000 and does not appear to be dose-related (Hay, 1985). Some transient abnormalities of liver function occurred in 50% of our patients but resolved despite continuation of therapy.

Fifty per cent of patients with progressive hormonally unresponsive prostatic cancer will die within 6 months.

Chemotherapy is not particularly effective and significant side effects are almost invariable in this elderly group of patients (Murphy, 1984). Significant objective benefit from aminoglutethimide is unusual and severe lethargy makes it unacceptable in many patients. We therefore feel that ketoconazole does have a role in this group of patients provided they are shown to have no pre-existing liver disease and that they are adequately monitored in specialist centres.

We cannot support the view of Trachtenburg and Pont (1984) for the use of ketoconazole as a single primary therapy because of its inadequate testosterone control in the intact male. It may have a role in combination with orchiectomy or an LHRH analogue aiming for total androgen ablation. These studies are under way.

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The Authors

Gordon Williams, FRCS, Consultant Urologist.
D. J. Kerle, FRCS, Senior Urological Registrar.
H. Ware, MB,BS, Senior House Officer, Department of Urology.
A. Doble, MB,BS, Senior House Officer, Department of Urology.
Helen Dunlop, BSc, Research Assistant, Department of Urology.
C. Smith, MA, MPhil, Research Assistant, Department of Urology.
Janet Allen, BSc, MRCP, Medical Registrar.
T. Yeo, BSc, PhD, Senior Biochemist, Department of Medicine.
S. R. Bloom, DSc, FRCP, Professor, Department of Endocrinology.

Requests for reprints to: Gordon Williams, Department of Urology, Hammersmith Hospital, Du Cane Road, London W12 0HS.

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Prostatic Carcinoma: Complications of Megavoltage Radiation Therapy

J. LINDHOLT and P. T. HANSEN

Department of Urology, Ribe County Hospital, Esbjerg, Denmark

Summary—Megavoltage radiation therapy and radical prostatectomy are at present the only curative treatments for prostatic carcinoma. Because a high complication rate appeared to follow radiotherapy, all patients with prostatic carcinoma presenting to a Danish provincial hospital between 1975 and 1980 were reviewed. Of 31 radiation-treated patients, 23 had serious complications. No recurrence was noted in eight patients. Twenty-three had a recurrence despite radiotherapy but 11 of these patients had no local recurrence. In view of the high level of complications following radiation therapy and the high incidence of latent carcinomas in the prostate gland, a cautious approach to radiotherapy is recommended.

Megavoltage radiation therapy has over the past 15 or 20 years been increasingly used as an alternative to oestrogens in the treatment of prostatic carcinoma (Edsmyr *et al.*, 1973; Bagshaw *et al.*, 1977). Although a common disease, its treatment is controversial, for only a small percentage of patients die from it. On the other hand, death from prostatic carcinoma forms a high proportion of cancer deaths in many countries, and this has led to a more aggressive attitude towards its treatment.

Most investigations on the effects of radiotherapy have shown promising results, but the prolonged survival of patients with prostatic carcinoma makes evaluation of the results difficult.

We felt that radiotherapy impaired the quality of life in many cases because it frequently led to gastrointestinal and urological complications. All cases of prostatic carcinoma treated over a 5-year period were therefore reviewed in order to assess the number and gravity of complications following radiotherapy.

Patients and Methods

Between 1975 and 1980, 87 men aged between 47 and 89 years (mean 70) were admitted with a diagnosis of prostatic carcinoma. Their case notes were reviewed and they were followed up until January 1983, partly through their General Practitioner and partly through subsequent hospital admissions resulting from recurrence of disease or complications of radiotherapy. Of the 31 patients who underwent megavoltage radiation 25 were aged less than 70 years and the rest were aged between 70 and 80.

The diagnosis was established by histological examination of tissue removed during transurethral resection of the prostate. The patient was then evaluated by the urologist and the radiotherapist,

Table Details of Complications

Complications	*Number*
Chronic cystitis	3
Clot retention	1
Thimble bladder	2
Urethral stricture	1
Chronic proctitis	5
Anal incontinence	1
Rectal tenesmus	2
Vesico-abdominal fistula	2
Persistent diarrhoea	5
Necrosis of caput femoris and acetabulum	1
	23

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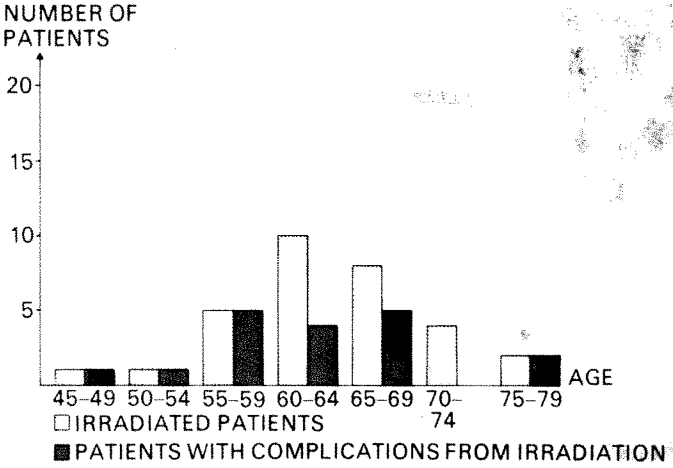

Fig. 1 Irradiated patients and those with complications in relation to age.

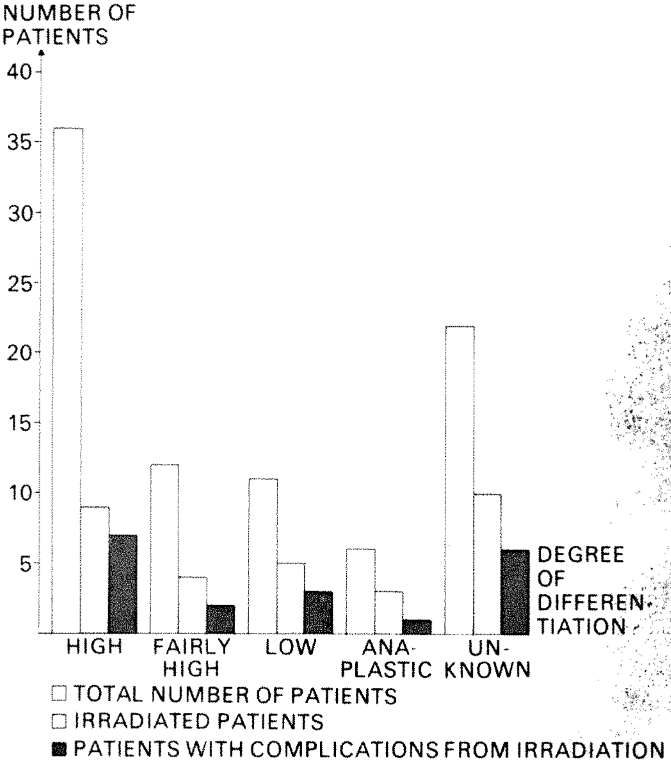

Fig. 2 Total number of patients, irradiated patients and those with complications related to the degree of tumour differentiation.

having been examined by bone scintigraphy, X-ray of thorax, pelvis and vertebral column and by intravenous urography. Lymphography was not performed. Only patients with local disease underwent radiotherapy. The degree of tumour differentiation and the age of the patient were also taken into account.

The 31 patients who underwent radiotherapy were all treated by the same technique, *i.e.* irradiation of the pelvis (using two fields) twice weekly for 3 weeks; this was repeated after a 3-week interval. The total dose was 62 Gy.

Results

Only major complications requiring hospital admission were considered (Table). Seventeen of 23 patients (74%) had complications lasting more than 3 months. Six patients (19%) had disabling sequelae such as necrosis of the caput femoris, fistulas (vesico-abdominal) and "thimble" bladder. As shown in Figure 1, there was no relation between age and number of complications. Figure 2 shows the degree of differentiation of the tumours in relation to the total number of patients, the number of irradiated patients and the number of patients with complications.

The benefit to the patients was evaluated in terms of absence of local recurrence and also in relation to cure of the disease. Local recurrence was defined as invasion of the bladder and the need for drainage, together with histological verification. Spread of disease was confirmed by X-ray or bone scintigraphy. In 8 of 31 cases (26%) no recurrence (either local or metastatic) was demonstrated. Eleven patients (35%) developed metastases without local recurrence and 12 patients (39%) developed local recurrence, with or without metastases.

Discussion

Radical prostatectomy and megavoltage radiation are probably the only curative treatments for prostatic carcinoma. The recurrence rate found in the present study (23 of 31 patients) is in agreement with the findings of Schønsted-Madsen (1979) and Sell (1979). Our high recurrence rate may be attributed to our conservative approach towards radiation treatment of highly differentiated tumours (Fig. 2), which usually have a longer survival rate. Of the eight radiation-treated patients with no evidence of recurrence, six had highly differentiated tumours, which suggests that it is the autonomous characteristics of the tumour rather than the effects of irradiation that decide the time of recurrence. On the other hand, radiation therapy may have a beneficial effect on local control of tumour, since 11 of 23 patients with evidence of progression had only distant metastases. The patients in this series did not undergo lymphography prior to radiotherapy, and several patients probably had spread of disease at the time of treatment.

The longer-lasting complications in this series were considerably more frequent than those reported by Gadeberg and Sell (1978) and Schønsted-Madsen (1979). The patients were highly selected and generalisations cannot be made, but the high level of complications should suggest a more restrictive use of radiotherapy. Termansen and Thybo (1970) found the same 5-year survival rate for patients with benign prostatic hypertrophy as for those with prostatic carcinoma stages I and II.

In future the aim should be to select the aggressive prostatic tumours, so that patients with the more harmless forms of prostatic carcinoma are spared unpleasant treatment. Furthermore, candidates for radiotherapy should be examined by means of X-ray, lymphography and biopsy of lymph glands (in addition to those investigations previously described), so that patients with metastases are not irradiated.

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The Authors

J. Lindholt, MD, Senior Registrar.
P. T. Hansen, MD, Senior Registrar.

Requests for reprints to: J. Lindholt, Department of Urology, Ribe County Hospital in Esbjerg, 6700 Esbjerg, Denmark.

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Epidermoid Cyst of the Testis: a Critical Analysis

R. S. MALEK, J. S. ROSEN and G. M. FARROW

Departments of Urology and Pathology, Mayo Clinic and Mayo Foundation, Rochester, USA

Summary—Our experience with 163 patients (11 from our institution) with simple epidermoid cyst of the testis was analysed. The lesion is nearly as common as interstitial cell tumour of the testis. In its simple form it is a benign lesion that usually appears as a solitary, asymptomatic, testicular, 2-cm mass in non-black young men (usually 20 to 40 years of age). It has been suspected on circumstantial clinical evidence in a few patients (17.5%) who have been successfully treated by simple enucleation. In the majority, however, fear of looking for a zebra in a herd of horses or not thinking of zebras at all has led to radical orchiectomy. None of the 80 patients followed up for a maximum of 37 years has suffered any ill effects.

Epidermoid cyst of the testis has evolved from a benign curiosity into a not uncommonly encountered testicular lesion over the last four decades. Throughout this period the histogenesis, behaviour and, hence, the treatment of this lesion have been the subject of controversy.

In an attempt to resolve some of these controversies we reviewed a group of patients with epidermoid cyst of the testis seen at our institution. Our findings with regard to these patients, together with a critical analysis of the literature, are presented.

Patients and Methods

Eleven cases of epidermoid cyst of the testis were encountered among nearly 1130 cases of surgically treated testicular tumours (1%) seen in a 76-year period (1907-1983). Four of these cases (nos. 1-4, Table 1) had been reported previously (Dockerty and Priestley, 1942; Gilbaugh *et al.*, 1967). Additional follow-up on these four cases and details pertaining to all 11 cases are summarised in Table 1.

All of the patients were white. Their ages ranged from 15 to 63 years (mean 34.5 years). All lesions were painless and were discovered by the patient palpating a testicular mass or on routine medical examination. The lesions ranged from 1 to 3 cm (mean 2 cm) in diameter, they were on the right side in five patients and the left side in six, and they occupied the following locations in the testis: upper pole, 2; lower pole, 4; and elsewhere within its substance, 5.

Nine patients were treated by simple or radical inguinal orchiectomy. In the remaining two patients, enucleation of the lesion was carried out; one of these (case 5), a 49-year-old, had a testicular mass that had been present, unchanged, for 8 years. All patients remained in good health during follow-up (6 months to 37 years; mean 10.8 years); one (case 3) died in a motor vehicle accident.

Discussion

Ewing (1940) originally described two examples of squamous epithelial "rests" in the testis. Later, in 1942, Dockerty and Priestley amplified and clarified the definition of this lesion by reporting a case (case 1, Table 1) which they called "undoubtedly benign, pure epidermoid cyst completely encased within the body of an otherwise normal testis". Since then, 155 cases, including 3 of ours (cases 2-4), have appeared in the literature (Goldstein *et al.*, 1980; Goli *et al.*, 1980; Bates *et al.*, 1981; Shah *et al.*, 1981; Godec *et al.*, 1982; Rao and Lorimer, 1982). To these we add 7 new cases (cases 5-11) and bring the total up to 163 cases.

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Table 1 Mayo Clinic Series, 1907-1983

Case	Age (yr)	Side	*Lesion* Size (cm)	Location	Operation	Length of follow-up (yr)*
1	35	R	2.0	Central	Simple orchiectomy	37
2	27	R	2.0	Lower pole	Simple orchiectomy	17
3	33	R	1.5	Central	Enucleation	6
4	15	L	1.5	Lower pole	Inguinal orchiectomy	2
5	49	R	1.0	Medial	Enucleation	23
6	18	R	2.5	Lower pole	Inguinal orchiectomy	0.5
7	51	L	3.0	Central	Inguinal orchiectomy	12
8	55	L	3.0	Upper pole	Inguinal orchiectomy	9
9	15	L	1.0	Central	Inguinal orchiectomy	8
10	18	L	3.0	Lower pole	Inguinal orchiectomy	3
11	63	L	2.0	Upper pole	Inguinal orchiectomy	1

* All patients were in good health at follow-up. In case 3, patient died in motor vehicle accident. Cases 4 and 6 were lost to further follow-up.

Table 2 Review of the Literature (Goldstein *et al.*, 1980; Goli *et al.*, 1980; Bates *et al.*, 1981; Shah *et al.*, 1981; Godec *et al.*, Rao and Lorimer, 1982) and Present Series

Feature	No. of Cases	*Cases affected* No.	%
Age	160		
2nd-4th decades		138	86
3rd decade		81	51
Race	104		
White		92	88
?Oriental		12	12
Presentation	154		
Self or medical exam		122	79
Discomfort		28	18
Cryptorchid		3	2
At autopsy		1	< 1
Side involved	155		
Right		83	54
Left		71	46
Bilateral		1	< 1
Treatment	160		
Orchiectomy		132	82
Enucleation		28	18

Some of the features of the patients (including ours) about which data were available are summarised in Table 2. From an in-depth review of the literature and our experience it appears that epidermoid cyst of the testis occurs as a solitary lesion. It accounts for nearly 1% of all testicular tumours and is thus almost as common as the interstitial cell tumour of the testis (Shah *et al.*, 1981). Clinically, most epidermoid cysts of the testis (86%) occur in young men in the second to fourth decades of life but neither the young nor the aged are spared (age range 3 to 77 years) (Goldstein *et al.*, 1980; Goli *et al.*, 1980; Bates *et al.*, 1981; Shah *et al.*, 1981; Godec *et al.*, 1982; Rao and Lorimer, 1982). Thus far, only whites or Orientals have been affected (Goldstein *et al.*, 1980; Shah *et al.*, 1981). Most of the lesions (79%) are detected by self-examination or on routine physical examination. A few (18%) come to light because of discomfort (Goldstein *et al.*, 1980; Goli *et al.*, 1980; Bates *et al.*, 1981; Shah *et al.*, 1981; Godec *et al.*, 1982; Rao and Lorimer, 1982) (a 14-year-old was thought to have torsion (Goldstein *et al.*, 1980)), and occasionally (2%) they are found in cryptorchid testes. The simple lesions are usually 2 cm in diameter (range 0.5-10.5 cm) (Goldstein *et al.*, 1980; Goli *et al.*, 1980; Bates *et al.*, 1981; Shah *et al.*, 1981; Godec *et al.*, 1982; Rao and Lorimer, 1982). They apparently have no predilection for central-hilar parts rather than polar regions of the testis (Price, 1969; Shah *et al.*, 1981) but involve the right testis a little more frequently than the left (54% *vs.* 46%) (Goldstein *et al.*, 1980; Goli *et al.*, 1980; Bates *et al.*, 1981; Shah *et al.*, 1981; Godec *et al.*, 1982; Rao and Lorimer, 1982); one patient has had the lesion bilaterally (Shah *et al.*, 1981). Interestingly, two patients had Klinefelter's syndrome (Goldstein *et al.*, 1980; Shah *et al.*, 1981), one had Gardner's syndrome (Shah *et al.*, 1981), and another had a microscopic focus of primary carcinoid tumour in the cyst wall (Goldstein *et al.*, 1980).

The diagnosis of a lesion as a simple benign epidermoid cyst of the testis is confirmed pathologically when the following five criteria set by Price (1969) are met: (1) the lesion is a cyst located within

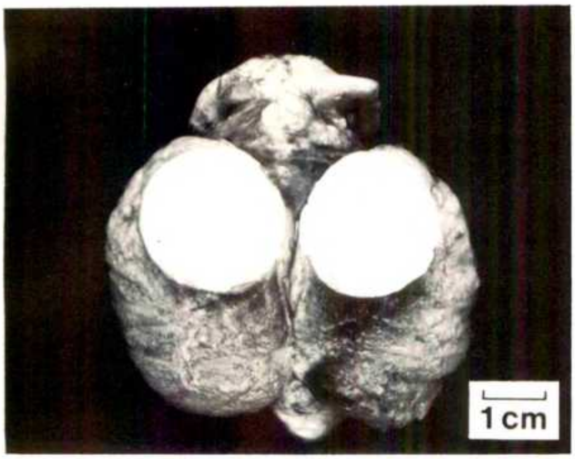

Fig. 1 Epidermoid cyst. The lesion is located entirely within the testis and is filled with keratinised debris.

the parenchyma of the testis (Fig. 1); (2) the lumen is filled by keratinised debris; (3) the wall of the cyst is composed of fibrous tissue with complete or incomplete lining of squamous epithelium (Fig. 2) (the wall frequently contains areas of calcification and, rarely, ossification (Price, 1969)); (4) no teratomatous elements or dermal adnexal elements such as sebaceous glands or hair follicles are present, either within the cyst wall or elsewhere within the parenchyma of the testis; (5) no scar is present in the remaining testicular parenchyma.

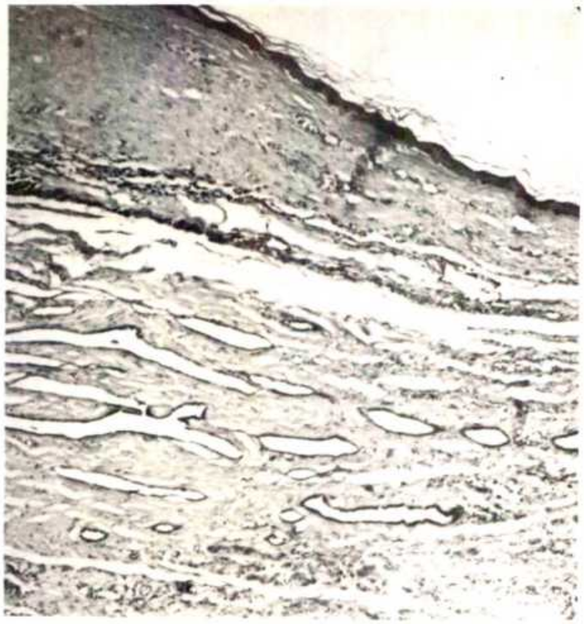

Fig. 2 Histological section of cyst in Figure 1. The cyst, adjacent to the compressed rete testis, is lined by keratinising epithelium. (H and E × 40).

Strict adherence to these criteria clearly separates *simple* benign unidermal *epidermoid* cysts (Dockerty and Priestley, 1942) from two dangerously confusing situations. One is the more complex bidermal or tridermal testicular teratomas, all of which have malignant potential and among which one observes the rare *dermoid* cyst (Dockerty and Priestley, 1942). This latter tumour commonly contains hair follicles (Fig. 3) and sebaceous glands as well as other endodermal and mesodermal elements (Dockerty and Priestley, 1942); it should not be confused with epidermoid cyst. The other situation is the rare instance (five cases, not included in this series) of widespread metastatic germ-cell carcinoma. In each of these, on retrospective examination a burnt-out primary scar was found in the same testis that contained one or two tiny (3-4 mm) epidermoid cysts as well (Azzopardi *et al.*, 1961; Weitzner, 1964; Price, 1969; Shah *et al.*, 1981).

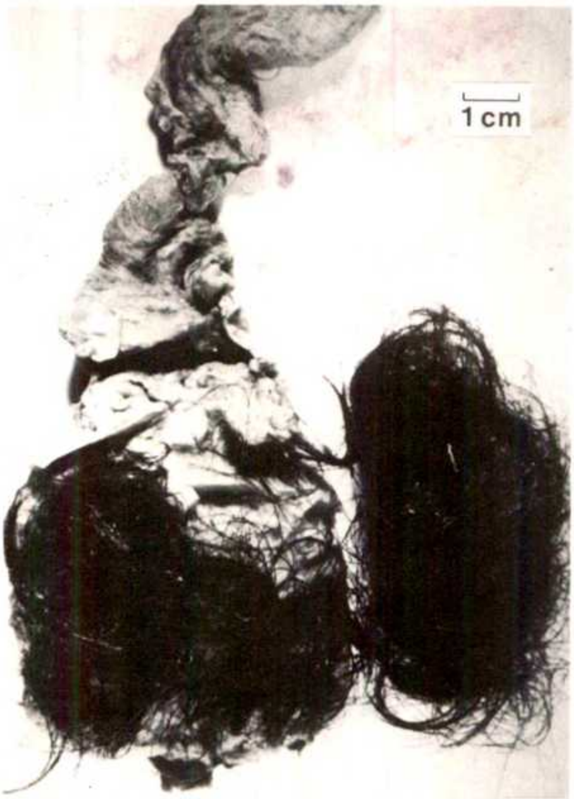

Fig. 3 Dermoid cyst of the testis, producing an abundance of hair. (From Dockerty and Priestley (1942). By kind permission of the Williams and Wilkins Company).

Histogenesis of the epidermoid cyst of the testis has been explained by several theories: squamous metaplasia of the rete testis (Halley, 1961) or of the seminiferous epithelium (Olsen and Calderin, 1955), inclusion of epidermal cysts (Weitzner, 1964) and, the most widely accepted, the cyst is the end result of the monomorphic development of a teratoma along the line of epidermal differentiation (Weitzner, 1964; Price, 1969; Shah *et al.*, 1981). The reasons for such wide acceptance have been stated by Shah *et al.* (1981) and relate to certain similarities between the development of epidermoid cysts and germ-cell tumours of the testis. They include age range, rarity of occurrence in blacks, more frequent occurrence on the right side, mirror occurrence of epidermoid cysts in the ovary, and occurrence in cryptorchid testes.

Treatment of epidermoid cyst of the testis has varied a great deal. One-fifth of the patients have undergone local excision (enucleation) of their lesion without any ill effects (Table 2). The remainder have been treated by simple or radical orchiectomy because of fear of malignancy and, indeed, several patients have been subjected subsequently to retroperitoneal node dissection (Price, 1969; Goldstein *et al.*, 1980). Altogether, 80 patients have been followed from 1 month to 37 years (Shah *et al.*, 1981, and present series); all have remained in good health. Of the six who died 1 to 6 years postoperatively (Shah *et al.*, 1981), none had any ill effect related to the testicular lesion.

Three factors appear to have been responsible for the more aggressive forms of therapy. First, the lesion is uncommon and therefore rarely thought of in the differential diagnosis of a testicular mass. Furthermore, not only is there no reliable diagnostic technique for its accurate recognition pre-operatively, but matters are made worse by the fact that it actually has many clinical features in common with the germ-cell tumours. Second, some clinicians may confuse the simple benign epidermoid cyst of the testis with the dermoid, both of which were introduced into the urological literature by Dockerty and Priestley (1942), or with other more complex bidermal or tridermal teratomas that clearly have malignant potential (Dockerty and Priestley, 1942; Price, 1969; Goldstein *et al.*, 1980). Indeed, the confusion continues in the urological literature (Rifkin and Jacobs, 1983). Third is the spectre of the five patients who died with widespread metastatic germ-cell carcinomas (Azzopardi *et al.*, 1961; Weitzner, 1964; Price, 1969). Clearly, the clinical significance of the tiny (3-4 mm) impalpable, asymptomatic epidermoid cysts found retrospectively in the same testis that contained the scar of the presumed burnt-out tumours in these five patients is not at all the same as that of the 163 solitary, palpable, simple cysts reviewed in this report. It is true that epidermoid cysts do develop as a unidermal expression of a germ layer and can be present as minor or major components of teratomas (Price, 1969), but these mixed epidermoid cysts then do not fit into the pathological definition of the simple ones to which authors from this institution and elsewhere have been referring for 41 years (Ewing, 1940; Dockerty and Priestley, 1942; Gilbaugh *et al.*, 1967; Price, 1969; Goldstein *et al.*, 1980; Goli *et al.*, 1980; Bates *et al.*, 1981; Shah *et al.*, 1981; Godec *et al.*, 1982; Rao and Lorimer, 1982).

Preservation of the testis, especially in a young man, is highly desirable. Therefore, if the patient has had an unchanging solitary testicular mass for several years and if there is no clinical, radiographic or biochemical (tumour-markers, *etc.*) evidence for malignant testicular disease, a conservative procedure (enucleation) via the inguinal approach with proper safeguards and without sacrificing the principles of cancer surgery seems justified (Gonzalez and Ross, 1977; Godec *et al.*, 1982; Rao and Lorimer, 1982) (case 5, Table 1). If immediate examination of the enucleated lesion leaves the pathologist in doubt or if, before enucleation, more than one lesion is suspected, then radical orchiectomy should be carried out immediately at the same sitting. In most cases there is no clear and reliable history or findings. Under these circumstances we fully subscribe to Donohue's recommendation: "when in doubt, take it out—properly" (Donohue, 1980).

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The Authors

R. S. Malek, MD, MS, FRCS, FACS, Consultant, Department of Urology.

J. S. Rosen, MD, Chief Resident Associate, Department of Urology.

G. M. Farrow, MD, MS, Chairman, Department of Pathology.

Requests for reprints to: R. S. Malek, Department of Urology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

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Bilateral Malignant Testicular Germ Cell Cancer

S. KRISTIANSLUND, SOPHIE D. FOSSÅ and K. KJELLEVOLD

Departments of General Oncology and Pathology, Norwegian Radium Hospital, Oslo, Norway

Summary—Twenty-six of approximately 1300 patients (1.9%) with unilateral testicular cancer developed a second primary germ cell cancer (seminoma 18; non-seminoma 8). Patients with previous seminoma had a significantly higher risk of developing a new seminoma than those with a previous non-seminoma. The diagnosis of second primary was made within 3 years of the first diagnosis in only 50% of the patients. In patients with a history of undescended and/or atrophic testes the interval significantly decreased between the diagnosis of the two testicular cancers.

The prognosis of bilateral testicular cancer is generally good. Patients in whom the second testicular cancer is at clinical stage I (no metastases) at diagnosis can safely be observed without further treatment after orchiectomy.

A patient with unilateral testicular cancer should be informed of the increased risk of developing a second primary germ cell tumour and should be encouraged to perform regular examination of the remaining testis. The need for life-long follow-up visits for patients with testicular cancer is questionable.

It is recognised that patients with testicular cancer have an increased risk of developing a new primary malignant germ cell tumour on the contralateral side (Hamilton and Gilbert, 1942; Aristizabal *et al.*, 1978; Sokal *et al.*, 1980; Bach *et al.*, 1981; Ware *et al.*, 1982). However, only a few larger series (with more than 20 cases) have been published from a single institution. The aim of the present study was to summarise observations from The Norwegian Radium Hospital in patients developing bilateral testicular germ cell cancer, especially as regards risk factors and histology.

Patients and Methods

During the years 1956 to 1980 about 1300 patients with newly diagnosed testicular cancer were admitted to The Norwegian Radium Hospital, representing about 90% of all new cases diagnosed in Norway during this period. Most of the patients received radiotherapy, supplemented or replaced by available chemotherapy in patients with distant metastases. With this treatment the 1- and 3-year crude survival rates for all 1300 patients were 75 and 60% respectively (Cancer Registry of Norway, 1975, 1980), with a significant improvement after the introduction of cis-platin-based chemotherapy in 1978. Routine follow-up consisted of clinical, biochemical and radiological examinations at intervals of 2 to 4 months during the first 3 years, and then once or twice a year for 5 years.

In 26 of these patients (1.9%) a second primary testicular cancer was diagnosed. Table 1 summarises some of the clinical (Peckham *et al.*, 1981) and histopathological parameters (Mostofi and Sobin, 1977) for these patients. Nine patients had a history of undescended testis. In seven patients the remaining testicle was described as atrophic at the time of diagnosis of the first primary.

One patient had three brothers who had also been treated for testicular cancer. Otherwise there was no increased frequency of testicular or ovarian cancer among the patients' relatives. Only one patient had a history of orchitis.

Results

Histology

The second testicular cancer was a seminoma in 18

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Table 1 Details of 26 Patients with Bilateral Testicular Germ Cell Cancer

First cancer		*Second cancer*	
Mean age (years)	33.5		38.0
Histology			
Seminoma	14	Seminoma	13
		Non-seminoma (ES + S)	1
Non-seminoma*	11	Seminoma	5
		Non-seminoma	6
Malignant germ cell tumour, type not assessable	1	Non-seminoma (ES)	1
Stage I	20		22
II	1		1
III	—		1
IV	4		2
Unknown	1		—
Treatment after orchiectomy			
Radiotherapy	18		12
Chemotherapy (± retroperitoneal surgery ± radiotherapy)	5		3
No treatment	3		10
Retroperitoneal surgery			1

E = embryonal carcinoma. S = seminoma, T = teratoma. EnS = endodermal sinus tumor.
* 1 E + S → E + S + T; 2 E + T → E; 3 E + T → E + T; 4 E → mature T; 5 EnS → T + S; 6 T + E → T + E; 7 S + T → S; 8 immature T → S; 9 E → S; 10 immature T → S; 11 E + S → S.

Table 2 Interval between First and Second Orchiectomy

	Interval (months)		
Type of Patient	*Mean*	*Median*	*Range*
All patients	68	41	0-324
Seminoma*	54	41	0-192
Non-seminoma*	58	29	2-197
Undescended testis			
Yes (9)	26	9	0-116
No (17)	91	96	0-324
Atrophic testis			
Yes (7)	7	2	0-20
No (19)	91	96	5-324

* Histological type of the first testicular tumour not assessable in one patient with an interval of 324 months.

patients and a non-seminoma in 8 (Table 1). Of 14 patients with initial seminoma, 13 showed the same histology in the second primary. Five of 11 primary non-seminoma patients had a seminoma as the second testicular cancer. Thus patients with a seminoma at the first diagnosis had a significantly higher chance of developing a new seminoma than non-seminoma patients ($P < 0.05$, chi-squared test).

Interval between first and second primary tumour

The mean and median intervals between the first and second orchiectomy were 68 and 41 months respectively (Table 2). Two patients had their second primary cancer discovered at the time of the first orchiectomy. In 11 patients the second tumour developed during the first 3 years after treatment of the first testicular cancer. Thirteen patients had the second diagnosis made more than 5 years after the initial treatment, the maximal interval being 27 years.

In patients with a history of undescended and/or atrophic testes the mean interval between the first and second diagnosis was significantly decreased when compared with the mean interval in patients without these features ($P < 0.05$, Student's t test) (Table 2).

In 24 patients the diagnosis of the second primary tumour was made by the patient himself finding the new testicular cancer. The periodic examinations during follow-up raised no suspicion of a new testicular cancer before the patient himself had found the tumour in the remaining testis.

Stage

There was no marked difference in the stage distribution (Peckham *et al.*, 1981) between the first and the second testicular cancer (Table 1).

Treatment and Prognosis

A second course of radiotherapy was given to 12 patients (all clinical stage I) in whom the iliac lymph nodes on the side of the second testicular cancer had not been irradiated during the first course of radiotherapy. Ten patients without clinical or radiological evidence of metastases did not receive supplementary treatment after orchiectomy of the second testicular cancer (Table 1).

Three patients died of testicular cancer and in two of them it was the second primary. In the third patient it was not possible to decide whether the first or the second tumour was the cause of death. These patients had stage III or IV disease at the time of the treatment of the second testicular tumour.

Discussion

A proportion of patients with testicular cancer (1.5-3%) will develop a new primary tumour in the contralateral testis (Hamilton and Gilbert, 1942; Aristizabal *et al.*, 1978; Sokal *et al.*, 1980; Ware *et al.*, 1982). In comparison with the healthy male population, the risk is increased by a factor of 500 to 700 (Aristizabal *et al.*, 1978; Sokal *et al.*, 1980; Bach *et al.*, 1981; Wold and Tveter, 1981; Ware *et al.*, 1982). A second testicular cancer will probably occur more often in the future because the situation has changed since 1975 and 80 to 90% of patients are now cured after the first testicular malignancy.

The risk of developing a second malignant germ cell tumour is claimed to be especially high in patients who have or have had an undescended testis on one or both sides (Hamilton and Gilbert, 1942; Whitaker, 1970; Sokal *et al.*, 1980). The same is probably true of patients with an atrophic testis and in these patients the interval between diagnosis of the first and second testicular cancer is significantly decreased, as has been shown in the present study. Decreased fertility may be another risk factor. The reason for this increased risk of cancer in the remaining testis may be cancer *in situ*, the probable precursor lesion of a clinical germ cell tumour. Cancer *in situ* is particularly frequent in patients with previous unilateral testicular cancer, in subfertile and infertile males and in men with cryptorchidism (Berthelsen *et al.*, 1982; Skakkebaek *et al.*, 1982).

Several reports have emphasised the need for life-long follow-up of patients with testicular cancer in order to detect the second germ cell tumour at an early stage (Johnson and Morneau, 1974; Aristizabal *et al.*, 1978). The present report shows, however, that there is only a limited chance of diagnosing an asymptomatic second testicular cancer during routine follow-up. All of our patients with subsequent cancer found their second testicular tumour themselves before the diagnosis was made at a follow-up examination. If a patient with unilateral testicular cancer has been tumour-free for 3 to 5 years after the primary treatment, subsequent relapses are extremely rare. Routine follow-up examinations for control of the first germ cell tumour can be omitted or carried out infrequently. However, as Johnson and Morneau (1974) observed, as many as 50% of second testicular cancers develop after 3 years, sometimes after an interval of many years. At this time the patients are, if routinely controlled at all, seen by a doctor only once a year, an interval which is generally too long to allow early diagnosis of the second primary germ cell tumour which has not been discovered by the patient himself. On the other hand, relapse-free patients who have finished an intensive 3- to 5-year follow-up programme for a malignant germ cell tumour should be told of the increased risk of developing a second primary testicular cancer on the contralateral side and they should be encouraged to perform regular self-examination.

The prognosis for the second primary malignant germ cell tumour is usually good (Sokal *et al.*, 1980; Bach *et al.*, 1981). Most of the tumours are seminomas, particularly if the first tumour is also a seminoma. If possible, the principles of treatment should be the same as for malignant germ cell tumours. As a result of previous treatment there may, however, be difficulties, *e.g.* with radiotherapy or retroperitoneal lymph node dissection. In patients with clinical stage I the liberal use of a surveillance policy without treatment is justified. In patients with metastases, modern combination chemotherapy should be the basis of treatment.

It is concluded that at least 2% of patients with testicular cancer will develop a second primary testicular tumour. This percentage will probably increase. Patients with a history of testicular maldescent and/or an atrophic contralateral testis at the first diagnosis develop the second primary earlier than those without these characteristics.

There is no need for prolonged follow-up (more than 3-5 years) of relapse-free patients with unilateral testicular cancer in order to diagnose a second primary germ cell tumour at an early stage. The patient usually discovers the tumour himself.

Treatment of the second malignant germ cell tumour should follow the general principles of treatment for malignant testicular cancer, modified according to the previous treatment. Patients with a second testicular cancer clinical stage I can safely be observed after orchiectomy without further treatment. The prognosis for bilateral testicular cancer is good.

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The Authors

S. Kristianslund, MD, Health Assistant.
Sophie D. Fosså, MD, PhD, Senior Consultant.
K. Kjellevold, MD, PhD, Senior Health Officer.

Requests for reprints to: Sophie D. Fosså, General Department, Norwegian Radium Hospital, Montebello, 0310 Oslo 3, Norway.

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Bacterial Study of Clean Intermittent Catheterisation in Children

C. E. D. TAYLOR, GILLIAN M. HUNT and I. G. MATTHEWS

Clinical Microbiology and Public Health Laboratory, and Department of Urology, Addenbrooke's Hospital, Cambridge

Summary—Deterioration of the upper urinary tract is exceptional in children on clean intermittent catheterisation for neuropathic incontinence and is found only in those with pre-existing renal damage. This report describes a bacteriological study of 24 children, of whom 10 had renal damage and 14 did not have renal damage before clean intermittent catheterisation began. Boric acid was added as a preservative to samples of urine in preference to the use of dip-slides because it preserves pus cells as well as bacteria. The incidence of bacteriuria in the two groups was similar (78% of samples from those with, and 72% of samples from those without, pre-existing renal damage). The groups differed in that the urine of children in the group with pre-exising renal damage yielded organisms other than *Escherichia coli* more than twice as often as did the urine of those children without renal damage. Moreover, the children with pre-existing renal damage were more likely to have fever with urinary tract infection and some of them showed frequent changes of organisms in the urine. Whatever organism was present, however, children in the group with renal damage more often had heavy pyuria.

Clean intermittent catheterisation was originally introduced in an attempt to control incontinence in patients with neuropathic bladder (Guttmann and Frankel, 1966; Lapides *et al.*, 1972). Later, it was found to be of value in patients with functional obstruction to the outflow of urine from the bladder as well as in those with dilatation of the upper urinary tract or vesicoureteric reflux (Lyon *et al.*, 1975; Mulcahy and James, 1979; Kass and Koff, 1981; Eckstein and Molyneux, 1982; Scott and Deegan, 1982; Hunt *et al.*, 1984). Most of these patients benefit in terms of continence and in terms of maintaining a normal upper urinary tract or of improving a dilated one.

In children with spinal dysraphism, renal damage is often found to be associated with a palpably enlarged bladder which is caused by functional obstruction to urinary outflow and relates to the neural level of the spinal lesion (Withycombe *et al.*, 1978; Hunt *et al.*, 1981). Such neuropathic obstruction to urinary outflow, with or without vesicoureteric reflux and urinary infection, appears to be crucial in the aetiology of damage to the upper urinary tract. The relief of outflow obstruction, whether by sphincterotomy, vesicostomy or catheterisation, generally prevents deterioration of renal function. Those few who deteriorate are from the group of patients who had renal damage before clean intermittent catheterisation began (Drago *et al.*, 1977; Mulcahy and James, 1979; Eckstein and Molyneux, 1982; Crooks and Enrile, 1983).

In children with spinal dysraphism, clean intermittent catheterisation has been remarkably free of serious bacteriological complications. There has therefore been a singular lack of detailed bacteriological studies in such children. Any associated urinary tract infections, when they do arise, nearly always become asymptomatic after ensuring that the bladder empties completely and frequently (Lapides *et al.*, 1972; Kass *et al.*, 1981). In this study of children on clean intermittent catheterisation, serial catheter specimens were examined. A

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comparison was made between two groups of children, those with and those without pre-existing renal damage, in an attempt to identify any significant features in those with renal damage which imply a risk of further deterioration.

Patients and Methods

There were 23 girls and one boy. Their ages at the start of the study ranged from 6 months to 19 years (mean age 9 years 6 months). In 19 of the children, neuropathic incontinence was associated with myelomeningocele and in the other five with spina bifida occulta, spinal dysraphism, transverse myelitis, meningitis and spinal tumour.

The study lasted for 32 months. At the beginning of the study, 19 children were on intermittent catheterisation; five more were added and two discontinued during the course of the study.

Clinical evaluation

Before each child began clean intermittent catheterisation an intravenous urogram and a micturating cystogram were performed. Ten of the 24 children had renal damage consisting of severe dilatation of the upper urinary tract and three of them also had renal scars; 14 did not have renal damage. Three children in each group had vesicoureteric reflux (Table 1). An intravenous urogram was repeated at intervals. Renal function was assessed by clearance of ethylenediaminetetraacetate labelled with Cr51. The glomerular filtration rate so obtained was compared with that expected for a child of the same age according to data compiled by McCrory (1972) because comparison related to surface area of the child is meaningless in children as grossly deformed as were some of those in this study.

Table 1 Results of Intermittent Catheterisation

	Number	*Improvement*	*No change*	*Deterioration*
Pre-existing renal damage	10 (3)	1	8 (3)	1
No renal damage	14 (3)	0	14 (3)	0

Cases of vesicoureteric reflux in parentheses.

Catheterisation procedure

For the 22 older girls size 12 or 8 F stainless steel catheters were used. In the case of the baby girl a size 4 infant's plastic feeding tube was used as a urinary catheter. The one boy in this study used a soft rubber Jacques catheter size 10. Each mother was instructed (1) to wash her hands and the child's perineum before catheterisation; (2) to rinse the catheter in running tap water after use; (3) to boil the catheter in a saucepan of water; (4) to tip out the water and leave the catheter in the covered saucepan. In the case of the baby girl, the plastic feeding tube was not boiled but kept in a 0.0125% solution of sodium hypochlorite as used for babies' feeding bottles. If any child was going to be away from home for more than 4 h the boiled catheter was carried in a new plastic bag ready for use and a pre-packed "baby-wipe" taken for perineal toilet. The procedure was kept as simple as possible so as to ensure that each child was catheterised not less than 4 times a day.

Laboratory methods

Since many of the children lived far from the laboratory, their specimens had to be sent by post. Boric acid (0.5 g in each 28 ml specimen container) was used in preference to dip-slides or other methods because of its ability to preserve pus cells as well as bacteria (Porter and Brodie, 1969).

The average number of specimens per child was 16 (range 10-26). They were examined microscopically by means of a disposable cell-counting chamber (Hilson, 1964) and culturally on horse-blood agar and on cystine-lactose-electrolyte-deficient agar by the method of Leigh and Williams (1964) as well as by means of a standard loop technique. The number of pus cells and of bacterial colony-forming units per litre of urine was estimated and recorded.

Gram-positive cocci were identified by their colonial appearance and by the catalase test. Gram-negative aerobic bacilli were identified by their colonial appearance and were further characterised by the API 20E system and an antibiogram based on a disc-diffusion method. The API 20E system consists of 21 biochemical tests. Not only does it allow identification in terms of bacterial species, by means of a seven-digit profile, but small biochemical differences among strains allow changes in biotype within a species to be detected. The antibiogram was based on tests of susceptibility to six antimicrobial agents, namely ampicillin (20 μg), cephalexin (30 μg), sulphafurazole (100 μg), nitrofurantoin (50 μg), co-trimoxazole (25 μg) and nalidixic acid (30 μg). Changes in biotype and in the antibiogram of organisms isolated from specimens had to be consistent on at least two successive specimens before they were regarded as significant.

Results

Clinical

Febrile urinary tract infections were exceptional and arose in only six of the children, four of whom had pre-existing renal damage. Such episodes had been frequent and often prolonged in 12 children before starting clean intermittent catheterisation. The only children to show changes in the radiological appearances were two in the group with pre-existing renal damage. One of them improved, the other deteriorated (Table 1). Serial glomerular filtration rates were measured in 11 children; all of them remained stable. In three of these children renal function was already impaired before starting intermittent catheterisation. In the other eight it was normal.

Bacteriuria

From a preliminary study of 25 samples of urine, we confirmed that bacterial counts performed on those containing boric acid were not significantly different from those derived from the use of dip-slides. We also established that for practical purposes the numbers of viable bacteria remained constant and the pus cell count did not significantly change over a period of 3 days. In general, specimens arrived in the laboratory within 36 h.

Severe bacteriuria ($>10^8/1$) was found in 292/393 (74%) samples tested. It was similar in the two groups, being 78% in children with damaged kidneys and 72% in those with undamaged kidneys. There was, however, considerable individual variation as severe bacteriuria was found in all samples from five children (three of whom had renal damage) but in 10% or less of samples from two children (one of whom had renal damage). The range of organisms is shown in Table 2.

Escherichia coli was the organism found in 30% of samples from children with damaged kidneys and in 52% of samples from those with undamaged kidneys.

Organisms other than *E. coli* and mixtures of different organisms were found in 48% of samples from those children with renal damage but in only 20% of samples from those without renal damage. *Klebsiella*, *Pseudomonas* or *Proteus* species were found in 18% of samples from the children with damaged kidneys, but in only 5% of samples from those with undamaged kidneys.

Table 2 Range of Organisms ($>10^8/1$) Isolated from 292 Catheter Specimens

	Bacteria		*Number*	
Lactose fermenters	*Escherichia coli*		168	(57%)
	Coliform†		33	(11%)
	Klebsiella spp		20	(7%)
	Enterobacter cloacae		2	(1%)
	Providentia spp		1	
Non-lactose fermenters	*Pseudomonas spp*		14	(5%)
	Proteus spp		8	(3%)
	Staphylococcus albus		7	(2%)
	Enterococci		2	(1%)
Mixed cultures			37††	(13%)
	Escherichia coli	20 isolates		
	Coliform	8		
	Klebsiella spp	4		
	Pseudomonas spp	5		
	Proteus spp	6		
	Enterococci	13		
		Total	292	(100%)

† "Coliforms" were distinguished from *Escherichia coli* by their colonial appearance and antibiograms.

†† In three of the mixed cultures the organisms were not identified.

Changes of organism

Changes in species and biotype of organism were significantly more frequent in children with renal damage ($P<0.05$) (Table 3). API biotyping was done on most species of Gram-negative aerobic bacilli (*E. coli*, *Pseudomonas spp*, *Proteus spp*, *Klebsiella spp*, *Providencia spp*, and *Enterobacter cloacae*) isolated in numbers $>10^8/1$. In some children such organisms were rarely found but in 11 children there were at least ten samples from each that contained organisms for which an API profile was obtained. Most of these organisms were *E. coli*. Table 3 shows a tendency in any one child for the *E. coli* to revert to the same biotype after many months despite one or more changes in the meantime.

Pyuria

The cellular reaction to *Klebsiella spp*, *Pseudomonas spp* and *Proteus spp* was greater than that to *E. coli* and 35/42 (83%) samples with these organisms showed heavy pyuria ($>200\times10^6$ pus cells/1) compared with 78/168 (46%) of samples with *E. coli*. Although the cellular response appeared to be related to the species of the organism, the main difference was between the children with damaged

Table 3 Changes in Species and Biotype of Organisms

	Patient	*Number of samples*	*All changes of organism and biotype*	*Number of samples with* E. coli	*Number of changes in* E. coli *biotype*	*Persistence of single* E. coli *biotype in months*	
						Constantly	*Intermittently*
Pre-existing renal damage	1	21	6	2	0	1	—
	2	18	7	10	1	5	19
	7	16	4	12	2	4	11
	9	19	1	9	0	7	16
Total (mean)		74 (18.5)	18 (4.5)	33 (8)	3 (1)	17 (4)	46 (12)
No renal damage	11	21	3	17	1	10	22
	12	15	4	13	3	5	15
	13	22	3	18	1	7	14
	15	13	1	12	1	6	14
	16	22	5	11	1	11	24
	18	18	2	16	0	11	24
	19	19	1	17	0	10	21
Total (mean)		130 (18.5)	19 (2.5)	104 (15)	7 (1)	60 (9)	134 (19)
Significance of difference between damaged and undamaged kidneys:			χ^2 test $P<0.05$ (one tail)	χ^2 test $P<0.001$		Mann-Whitney U test $P<0.05$	Not significant $P=0.16$

and those with undamaged kidneys, whatever the organism. Severe bacteriuria (> 10^8/l) was accompanied by heavy pyuria in 64% of all samples from children with damaged kidneys compared with 39% of samples from children with undamaged kidneys (Table 4). This difference is reflected in the cellular response to *E. coli* bacteriuria, children with renal damage having heavy pyuria in 66% of samples compared with 38% in those without such damage. There were, however, notable exceptions. Two children, both with renal damage, never had heavy pyuria in any of 29 samples. In one of these, hydronephrosis improved dramatically.

Table 4 Bacteriuria (1) and Pyuria (2) Related to Pre-Existing Renal Damage

	Damage No. of samples	*No damage No. of samples*
Bacteriuria (1)	78% (129/165)	72% (163/228)
E. coli	30% (50/165)	52% (118/228)
Non-*E. coli*	48% (79/165)	20% (45/228)
Pyuria (2) with bacteriuria	64% (83/129)	39% (63/163)

Totals in brackets.
(1) $>10^8$/l
(2) $>200\times10^6$/l

Discussion

Early in this study we were concerned with the risk of introducing bacteria at each catheterisation. A girl with faecal incontinence might well be expected to contaminate the catheter while locating the urethral orifice in an anaesthetic perineum. Nevertheless, we did not find any association between faecal soiling or poor technique and either an increased incidence of bacteriuria or frequent changes in species or biotype of organism. On the other hand, as previously reported (Withycombe *et al.*, 1978), a somewhat higher incidence of severe bacteriuria was found in children who had a palpable bladder before clean intermittent catheterisation began (Table 5). In order to remain dry some children catheterised themselves more often or reduced their intake of fluid. The incidence of bacteriuria, however, was no higher in the latter than in those who drank more.

The mixed cultures containing two or three kinds of organism may indicate poor technique in catheterisation; 37 mixed cultures were obtained from 16 children. The prevalence of the organism found in the mixed cultures was similar to that in the pure cultures of only one species of organism except in two instances. (1) Enterococci were present in nearly half of the mixed cultures, whereas they accounted for only 1% of the pure cultures. (2) *Proteus spp* were found significantly more frequently in mixed than in pure cultures ($P<0.001$). With mixed as with pure cultures the incidence of bacteriuria bore no relationship to faecal incontinence.

Table 5 Palpability of bladder related to renal damage before starting intermittent catheterisation, and subsequent outcome. There was more renal damage in children with bladders palpable to the umbilicus ($P<0.05$) (cases of reflux in parentheses). ≥75% severe bacteriuria denotes that ≥75% of samples contained organisms $>10^8/1$. Wetness and an impalpable bladder are related ($P=0.002$ exact X^2, the baby* being excluded from the calculation).

Before starting intermittent catheterisation	Renal damage	7 (2)	3 (1)	0
	No renal damage	4 (1)	6 (2)	4
While on intermittent catheterisation	≥75% severe bacteriuria	8	6	1
	<75% severe bacteriuria	3	3	3
	Dry	8	6	0
	Damp	2	3	1
	Wet	1*	0	3

Although prophylactic antibacterial agents such as co-trimoxazole and nitrofurantoin had been used for varying periods in eight children, they were discontinued in all but one because they were found to be either unnecessary or ineffective. It was policy not to treat bacteriuria when asymptomatic but in practice a child was treated as the family doctor considered necessary. Some of the children were also under the care of orthopaedic and neurological surgeons as well as paediatricians who treated shunt infections, respiratory, and other infections to which these children are prone. Such treatment almost certainly had a secondary effect on the bacterial flora of the urine.

Since the children at risk of renal deterioration were those who had sustained damage before starting clean intermittent catheterisation, it is possible that the earlier introduction of catheterisation might have prevented damage. The success of catheterisation, however, depends largely on the enthusiastic co-operation of the mother and this is less likely to be forthcoming at an age when nappies are still acceptable. Usually, therefore, we have started catheterisation in the very young only when renal damage has already taken place. The collection of clean samples, which is easy in a catheterised child, is almost impossible in an incontinent girl and so we have relatively little bacteriological data before clean intermittent catheterisation began. Whether the increased incidence of non-*E. coli* bacteriuria, with its attendant resistance to antimicrobial agents, seen in some of these children preceded clean intermittent catheterisation, or whether it was the cause or effect of their renal damage remains unknown.

Clean intermittent catheterisation is particularly helpful in children with a large palpable bladder as they can be kept acceptably dry (Table 5). Moreover, such children are the ones most at risk of damage to the upper urinary tract and this may be prevented or improved by this procedure. Children on clean intermittent catheterisation sometimes have heavy pyuria and a preponderance of non-*E. coli* bacteriuria which is often multiply resistant to antibiotics. These two features together are usually associated with previous damage to the urinary tract and indicate a risk of further deterioration.

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The Authors

C. E. D. Taylor, MD, FRCPath, Consultant Microbiologist, Clinical Microbiology and Public Health Laboratory.

Gillian M. Hunt, MB, DCH, Clinical Assistant, Department of Urology.

I. G. Matthews, FIMLS, Chief Medical Laboratory Scientific Officer, Clinical Microbiology and Public Health Laboratory.

Requests for reprints to: C. E. D. Taylor, Clinical Microbiology and Public Health Laboratory, Level 6, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QW.

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An Experimental Study of Hydrophilic Plastics for Urological Use

J. W. A. RAMSAY, R. A. MILLER, P. R. CROCKER, B. J. RINGROSE, S. JONES, D. A. LEVISON, H. N. WHITFIELD and J. E. A. WICKHAM

Departments of Urology and Histopathology, St Bartholomew's Hospital, Institute of Urology, London, and Royal Military College of Science, Shrivenham

Summary—Hydrophilic graft copolymers of polyethylene vinyl acetate (PEVA) were extruded into tubular form. These materials increase both external and internal diameters by 60% on contact with water. The tubes were used as ureteric stents in an experimental study and were superior to silicone stents of the same calibre in the limitation of urinary extravasation. Histological, cytotoxic and electron microscopic studies showed that PEVA is a biocompatible material suitable for clinical use in urology.

A biocompatible endoprosthesis which swells on contact with water may have wide clinical application as a catheter, drain or stent. Such an endoprosthesis would be secure and might limit the leakage of urine when placed in a damaged viscus. If the degree of swelling could be controlled, a viscus could be dilated by the insertion of such a prosthesis which would then act as a slippery conduit for endoscopic instrumentation.

Hydrophilic copolymers (Fydelor and Taylor, 1981) are made by a process of radiation initiation in which a hydrophilic substance, in this case acrylic acid, is grafted on to a pre-formed polyethylene copolymer (Fig. 1). The hydrophilic radicals (C00-) attract water which is absorbed on to the polymer, causing uniform swelling, and the remarkable property of an increase in both overall and internal diameter is thus achieved. The degree of swelling can be altered by the proportion of polyethylene to acrylic acid in the grafted substance. The rate of swelling can be controlled by the addition of a polyvinyl acetate coating which retards the rate of water absorption into the polymer.

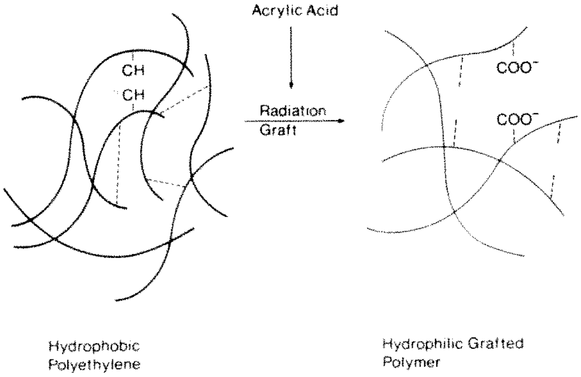

Fig. 1 The process of graft copolymerisation by radiation initiation.

We report our preliminary studies in the development of PEVA ureteric stents.

Material and Methods

Thirty-six minipigs were anaesthetised with halothane and the ureter exposed through an extraperitoneal loin incision.

Eighteen experimental procedures were undertaken using 4 F PEVA ureteric stents (Table). The contralateral ureter was used as a control. A similar number of procedures was undertaken using 5 F

Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

Table Ureteric Surgery Using PEVA Stents

Operation	*No.*	*Duration of intubation (weeks)*
Intubation alone	2	2
Uretero-ureterostomy	2	2
Intubated ureterotomy	10	1-6
Segmental ureteroplasty	4	1-6

standard pure medical grade silicone stents (polydimethylsiloxane). Figure 2 shows the experimental surgical model, comparing ureterotomy with a segmental ureteric replacement with a porcine dermal graft (Zenoderm). 6/0 Dexon or 8/0 Vicryl sutures were used throughout: 250 mg ampicillin were given intravenously per-operatively. An intravenous urogram was performed after 1 week to assess the degree of extravasation and to confirm the position of the stent. The animals were sacrificed 1 to 6 weeks following surgery: tissue was taken for histological examination, urine for microscopy and culture, and the stent was retrieved for scanning electron microscopy (SEM). Specimens for SEM were carbon coated in a Nanotech CC2 machine and placed in a JEOL 35 CF scanning electron microscope fitted with a backscattered electron detector, a Kevex Unispec System 7000 X-ray energy spectrometer, and a Dapple Microplus data processor. The surfaces were then examined in the secondary electron mode (SEI) and by the backscattered mode (BEI) at 25 kV. Areas of atomic number difference revealed by the BEI mode from particulate matter on the surface or within the lumen of the tubes were then analysed for their inorganic element content by X-ray energy spectroscopy (XES).

In order to study the surface detail of the tubes, further samples were prepared as above and gold coated in an Emscope SC500 gold coater and examined by scanning electron microscopy at 15 kV.

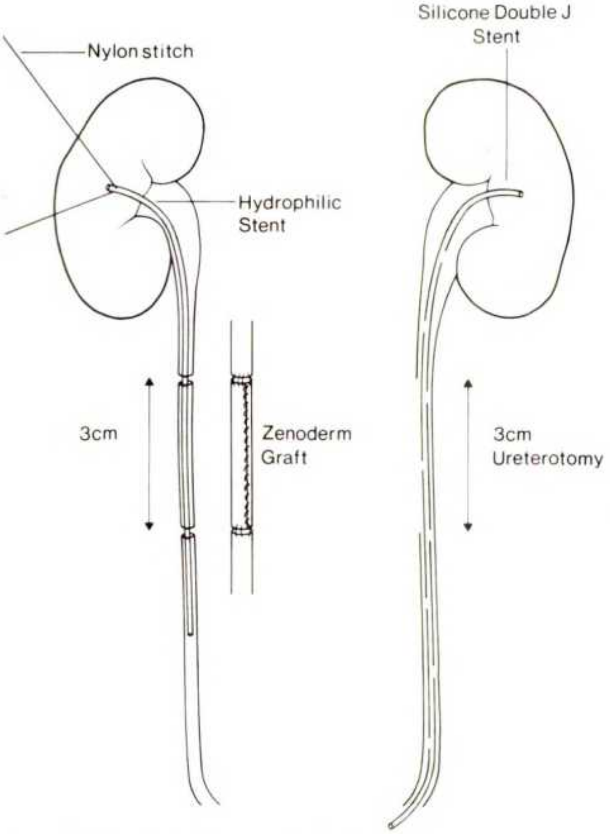

Fig. 2 Experimental surgical model.

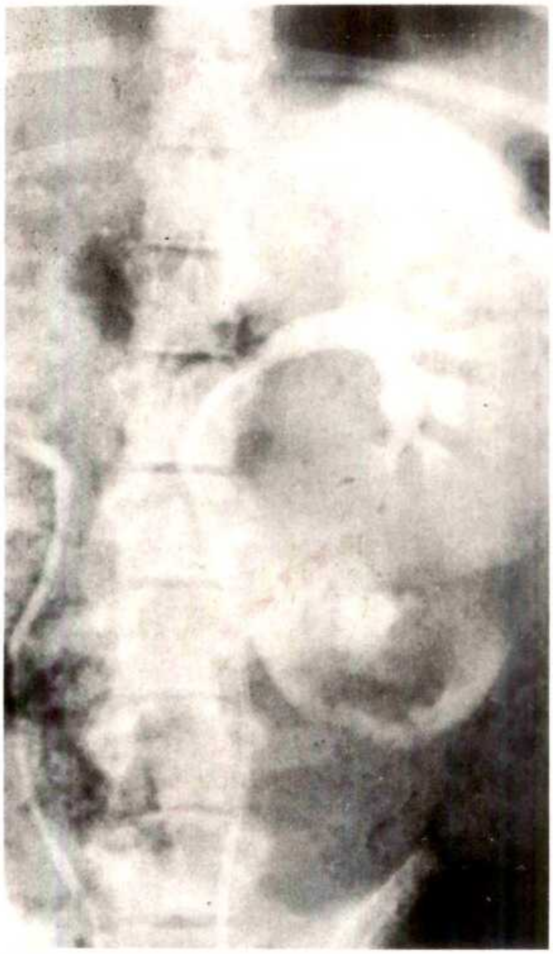

Fig. 3 A urinoma in association with a silicone stented ureterotomy.

Results

1. *Surgical Effect of PEVA Stents*

These stents limited urinary extravasation following ureterotomy. Extravasation with the formation of a urinoma was a constant finding in the ureters stented with silicone double J stents (Fig. 3).

2. *Histology*

Characteristic urothelial changes were seen in both the PEVA and the silicone stented ureters. The significance of these changes is unclear but they involved partial metaplasia to include numerous mucus producing cells (often swollen and vacuolated). Figures 4A and B show normal urothelium alongside urothelium which had been in contact with a PEVA stent for 6 weeks.

3. *Scanning Electron Microscopy*

The wet surface of PEVA compared favourably to the dry surface of pure medical grade silicone, before implantation (Figs 5A and B). Following 6 weeks' implantation there were no macroscopic encrustations on the surface of either material. Scanning electron microscopy of the PEVA tubes revealed a fine organic film with occasional small calcium crystals superimposed (Fig. 6).

4. *Bacteriology*

Two animals developed coliform urinary tract infection at 2 and 4 weeks respectively. Both animals had a urinoma surrounding a collagen ureteroplasty supported by a silicone stent. The presence of infection was not associated with more extensive mucous metaplasia or increased mucus production, and no encrustation occurred on the "infected" stents even when viewed by SEM.

Discussion

This study demonstrates the potential advantage of swelling stents in reconstructive ureteric surgery. The principle may have wider clinical applications, but because the increase in overall diameter may produce close application to epithelial and mucosal surfaces it is important to demonstrate the biocompatibility of this new material.

Biocompatibility in the urinary tract can be assessed in three ways:

1. The effect of the biomaterial on the urothelium.
2. The effect of urine on the biomaterial (disintegration).
3. The effect of the biomaterial on the urine (encrustation).

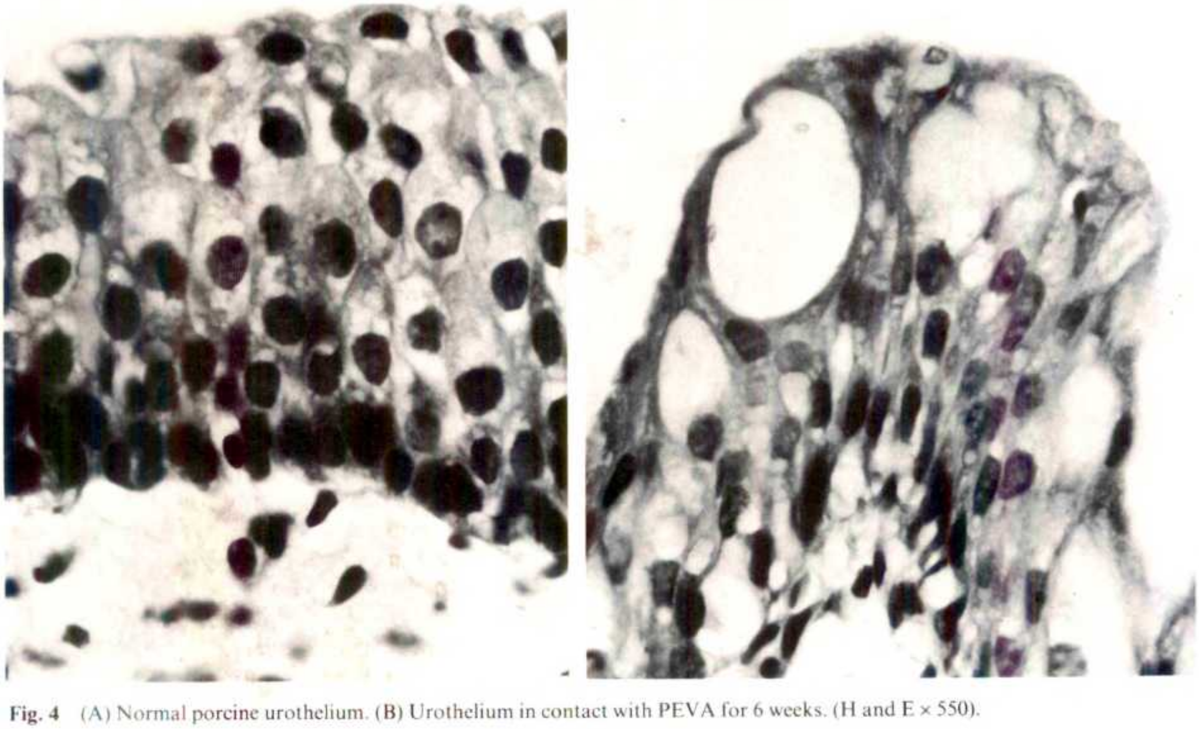

Fig. 4 (A) Normal porcine urothelium. (B) Urothelium in contact with PEVA for 6 weeks. (H and E × 550).

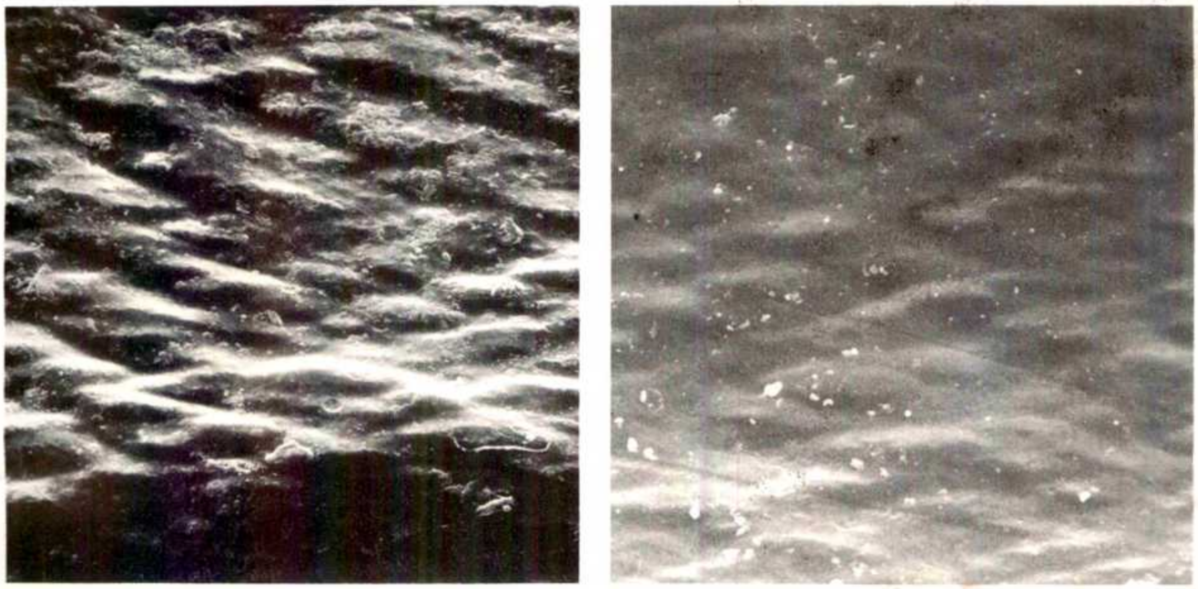

Fig. 5 Scanning electron micrographs of the surface of (A) dry and (B) wetted PEVA (× 250).

In experimental surgery this new material compares favourably with silicone, which is accepted as the most biocompatible material for long-term implantation. Biocompatibility is related to the smooth surface properties of plastics (Wilksch *et al.*, 1983; Ramsay *et al.*, 1985). However, Graham *et al.* (1984) have investigated the cytotoxicity of urinary catheters by various elution and onlay techniques. Cytotoxicity of plastics is usually caused by additives used for the manufacturing process. The additives are often referred to as "plasticisers" and consist of complex organic compounds. No plasticisers are used in the manufacture of PEVA. We have undertaken cytotoxicity studies by the elution method (Wilksch *et al.*, 1973), which is a most sensitive index of biocompatibility. PEVA produced cytotoxicity to cultured fibroblasts similar to that of siliconised latex. Interpretation of the clinical relevance of these studies is particularly difficult with hydrophilic materials because absorption of the fluid culture medium produces hypertonicity which *per se* may be cytotoxic to cultured cells. On the least favourable assessment of cytotoxicity, PEVA is no worse than medical grade siliconised latex; on this basis we have progressed to clinical trials. However, work continues to improve the methodology for cytotoxic testing of hydrophilic substances because the experimental evidence suggests PEVA to be as biocompatible as pure silicone.

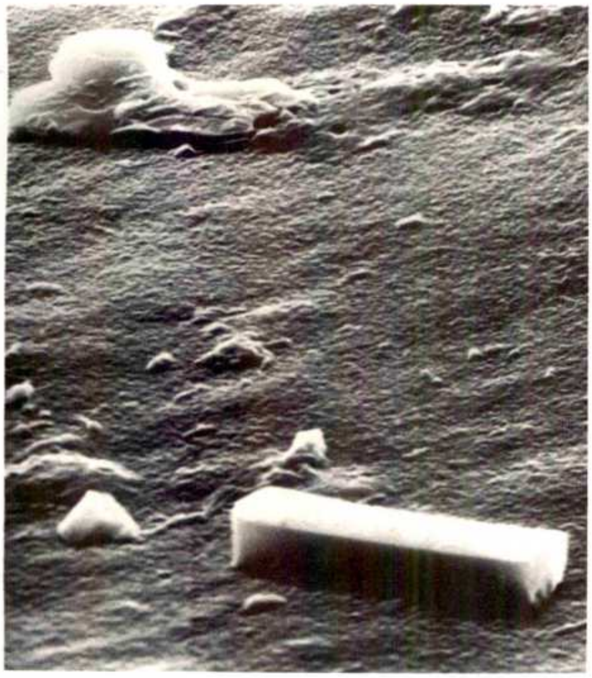

Fig. 6 Scanning electron micrographs of PEVA after 6 weeks' implantation (× 2000).

These experimental results confirm that the unique property of PEVA to swell in water is of value in reconstructive surgery. The material appears to have a high degree of biotolerance; the results of clinical trials are awaited.

Acknowledgements

We acknowledge the support of the Joint Research Board and Special Trustees of St Bartholomew's Hospital. Professor D. E. M. Taylor was responsible for the original studies in hydrophilic copolymers and has provided guidance and advice for the present study. The Royal Military College of Science deserve special recognition for the production of the prototype stents, catheters and dilators used in this project.

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The Authors

J. W. A. Ramsay, FRCS, Research Registrar, St Bartholomew's Hospital.

R. A. Miller, FRCS, Senior Urological Registrar, St Bartholomew's Hospital.

P. R. Crocker, FIMLS, Senior Chief Medical Laboratory Scientific Officer, Department of Histopathology, St Bartholomew's Hospital.

B. J. Ringrose, Technical Officer, Department of Applied Physics, Royal Military College of Science.

S. Jones, FIMLS, Senior Medical Laboratory Scientific Officer, Department of Pathology, St Bartholomew's Hospital.

D. A. Levison, MRCPath, Consultant Histopathologist, St Bartholomew's Hospital.

H. N. Whitfield, MA, MChir, FRCS, Consultant Urologist, St Bartholomew's Hospital.

J. E. A. Wickham, MS, FRCS, Director, Academic Unit, Institute of Urology.

Requests for reprints to: J. W. A. Ramsay, Department of Urology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

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Abstracts of the Proceedings of the Urological Society of Australasia, 38th Annual Scientific Meeting, Adelaide, Australia, 1985

President: J. S. Jose
Secretary: D. Golovsky
Editor: R. J. Millard

The 38th Annual General Meeting of the Urological Society of Australasia was held at the Hilton International, Adelaide, from 11 to 15 March 1985. The meeting was organised by Mr J. S. Jose, President of the Society, and a committee of local urologists. Principal guests at the meeting were Professor M. Marberger from Vienna, Professor W. Fair—Australian Kidney Foundation Visiting Professor for 1985 from New York, Dr P. Scardino of Houston, Texas, Professor M. S. Soloway from Memphis, Tennessee, and Professor F. Eisenberger from Stuttgart.

The programme included several papers from each of the principal guests on percutaneous nephrolithotomy, extracorporeal lithotripsy, and prostatic and bladder neoplasia. The Harry Harris Oration was delivered by Dr E. Hackett, a local physician and broadcaster, on the subject of "The Human Hand".

The Keith Kirkland prize for the best paper presented by a trainee was awarded to Dr B. Blyth of Christchurch, New Zealand. The President's Prize for the best paper, in a much enlarged section of the meeting, went to Mr. R. A. Gardiner for his poster "Immunohistochemical analysis of the human bladder".

The next annual scientific meeting will be held at the Sheraton Hotel, Perth, Western Australia, from 6 to 11 April 1986, under the presidency of Mr E. J. England.

Calculus Disease

Percutaneous Lithotripsy of Renal Calculi—Where We Stand Today

By M. Marberger
Rudolfstiftung, Vienna, Austria

Since 1980, 732 patients with renal calculi had percutaneous lithotripsy of renal calculi at this institution. With growing experience, a standardised approach based on a fine-needle nephrostomy technique, immediate tract dilatation with metal telescopic dilators, ultrasonic disintegration if necessary and short-term post-operative drainage with thin tubes, has evolved as the most successful technique.

There has been an overall success rate of 94%, no mortality or nephrectomy and an average time of hospitalisation of 4.7 days. Eighty-four percent of all renal calculi requiring surgical intervention were treated by percutaneous nephrolithotripsy in 1984. In the late follow-up of the first 82 patients there is no evidence of an increased rate of stone recurrence, infection, hypertension or morphological or functional deterioration of the kidney. Improvements in the endoscopic equipment and the liberal use of multiple nephrostomy tracts in one kidney have extended the range of the technique to branched stones and calculi in poorly accessible calices. The indication for the procedure in border-line cases depends upon the experience of the surgeon and his equipment and the time and patience invested in every case. The time factor appears to be the main limiting factor in extending this approach to all calculi.

The Problems and Complications of Percutaneous Nephrostomy

By I. N. Nunn
Royal Melbourne Hospital, Victoria

The problems and complications which occurred in the first 100 percutaneous nephrolithotomies performed at the Royal Melbourne Hospital are presented. Thirteen failures occurred mainly in the early part of the series and relate mainly to the lack of experience, particularly not being prepared to try a second time and lacking skills in tube and guide-wire manipulation. A second guide-wire was essential and allowed the collecting system to be recannulated if the track was inadvertently lost.

The 24 F nephroscope sheath considerably restricted the size of stone which could be extracted. The use of Amplatz sheaths of up to 35 F helped considerably and stones of 1.5 cm were removed intact. The size of the nephrostomy tract did not influence complications or the time taken for the track to close. Complex stones were extracted by multiple nephrostomies.

Complications were mostly minor, the most serious being a pelviureteric junction obstruction which resolved spontaneously following a small perforation. The incidence of residual fragments has become uncommon since we commenced using multiple nephrostomies and have been prepared to re-examine the collecting system if post-operative films show opacities of significant size to be still present.

Percutaneous Nephrostomy and Nephrolithotripsy: a Functional and Structural Analysis

By D. R. Webb and J. M. Fitzpatrick
Department of Urology, Meath Hospital, Dublin, Ireland

Before assessing percutaneous nephrolithotripsy, the effects of percutaneous nephrostomy alone must be known. We studied this by performing a nephrostomy and dilatation to 22 F in the left kidney of 15 dogs and flushing the formed tracks through the nephrostomy with 3 litres of urological glycine over 30 min. Ten were assessed at 48 hours and five at 6 weeks. Assessment was by bilateral creatinine clearance, vascular corrosion casting, IVU, microfil angiography, *ex situ* conventional angiography and digital subtraction angiography.

A 22 F nephrostomy caused no significant alteration in renal function. An initial small peripheral defect, involving the region of the track only, healed to a fine linear scar. No major vascular damage occurred with serial blunt dilation, this nephrostomy tract being equivalent to 35 F in man.

Having established that percutaneous nephrostomy alone did not damage the kidney significantly, a nephrostomy track of 24 F (corresponding to 38 F in man) was similarly created and human renal calculi placed in the renal pelvis via the nephrostomy track. Electrohydraulic nephrolithotripsy and ultrasonic nephrolithotripsy were performed under vision in eight dogs respectively; 5 of each group were evaluated at 48 h and 3 at 6 weeks, using the same modalities as for nephrostomy. Again, no significant alteration to renal function was detected with either procedure and a similar small track defect resolved to a fine scar with no major vascular damage. Scatter of minor stone fragments was observed on the endothelium but these did not embed in tissues and had disappeared at 6 weeks.

These experiments show that a large nephrostomy track created by serial dilatation does not disturb renal function and heals rapidly to a fine scar and that both electrohydraulic and ultrasonic nephrolithotripsy are safe procedures that do not significantly affect the kidney.

One-Stage Percutaneous Nephrolithotomy

By S. G. Stening
Royal Brisbane Hospital, Queensland

A personal series of percutaneous nephrolithotomy is presented whereby the aim has been to complete the procedure of needle access, track dilatation and removal of calculi in one stage with the urologist as the sole operator. Fifty-one patients were selected for treatment over a period of 18 months (one with bilateral calculi).

Needle access failed in 10, leaving 43 kidneys in which satisfactory access was obtained. Thirty-five of the 43 kidneys were radiologically and endoscopically cleared of all calculi, 29 in one stage. Six required a further stage for calculus clearance.

Four patients were incompletely cleared. In two of these patients the fragments were less than 5 mm in diameter and left to pass spontaneously. The remaining two retained calculi greater than 5 mm in diameter. In three patients calculi were inaccessible.

The site of calculi influenced the success of removal. All lower pole, compound and multiple calculi were removed, as were 14 of 15 renal pelvic calculi, once successful access was achieved.

With experience and selectivity, renal calculi can be successfully removed by percutaneous nephrolithotomy with the urologist operating alone, usually in one stage.

Percutaneous Nephrolithotomy—Experience in First 39 Cases

By A. N. James
Brisbane, Queensland

One-stage percutaneous nephrostomy, dilation and stone removal in 39 cases were carried out under general anaesthesia with fluoroscopic control by the author. The procedure involved the insertion of a ureteric catheter beforehand and the use of two guide-wires. The angle of puncture appeared to be critical.

Twenty-seven cases (70%) were successful. In the last 29 cases there were only 4 failures—a success rate of 86%. Good results were achieved in three solitary kidneys and in 11 kidneys previously subjected to open surgery. One patient required transfusion for a post-operative haemorrhage and one had a bacteraemia.

Specific problems of dislodged guide-wires, stones in adjacent calices and large stones were overcome by a variety of techniques. Total operating time was comparable to that of open surgery; 21 cases required less than 1½ h.

This technique carries the benefits of a shorter hospital stay, rapid post-operative recovery and earlier return to work.

Percutaneous Coagulum Lithotripsy: a New Approach

By M. Marberger, R. Hasun and J. M. Fitzpatrick
Rudolfstiftung, Vienna, Austria, and Meath Hospital, Dublin, Ireland

All techniques of intrarenal stone disintegration have a high risk of scattering stone fragments within the kidney, so that they cannot be removed. Attempts to solve the problem by trapping the fragments in a coagulum failed, mainly because of a high rate of complications.

We report *in vitro* studies using a new synthetic gel that liquefies completely at 37°C, yet forms a solid gel at slightly lower temperatures.

Calculi can be coated with this agent prior to their destruction, thus keeping the shattered stone fragments within the gel for ease of removal.

Acute and chronic *in vivo* experiments were performed to test the safety and efficiency of this approach. In 16 dogs a calculus was introduced into the renal pelvis through a nephroscope. It was then coated with the gel by using cooled irrigation fluids and destroyed by electrohydraulic lithotripsy. The dispersion of fragments was successfully prevented and a spectrum of functional and morphological studies revealed no evidence of topical or systemic toxicity, of intrarenal gel residuals or of pulmonary or peripheral embolisation.

Adapted to clinical practice, this technique could solve the problem of stone residuals of percutaneous nephrolithotripsy when performed alone or in combination with extracorporeal shockwave lithotripsy.

Non-Invasive Renal Stone Therapy with Extracorporeal Shockwave Lithotripsy—Clinical Experiences and Results

By F. Eisenberger, G. Fuchs and K. Miller
Stuttgart, West Germany

Extracorporeal shockwave lithotripsy (ESWL) is the non-invasive treatment for urinary stones and has been in clinical use for more than 3 years. In the last 12 months more than 800 treatments have been carried out in our department. The range of indications, which previously had included approximately 70 to 80% of all stone patients, can now be extended by combining ESWL and endo-urological methods such as percutaneous nephrolithotomy (PCN) and ureteroscopic stone manipulation (URS).

The success rate for ESWL alone was 98.4%. No damage to kidneys or adjacent organs was detected in these patients and renal function was unaltered. Problems may occur after successful disintegration during the period of spontaneous stone passage, 16% requiring auxiliary measures to relieve obstruction or to remove stone debris. On re-evaluation, 85% of patients were stone-free and 14% had residual fragments, 11% of which are judged to be spontaneously passable.

ESWL and endo-urology have revolutionised our management of calculi; only 6% of 1300 consecutive stone patients required open surgery.

Strategy for Stone Management

By D. R. Webb, S. R. Payne, G. Watkinson and J. E. A. Wickham
Devonshire Hospital Lithotripter Centre, London, UK

Extracorporeal shockwave lithotripsy (ESWL) forms the basis of treatment for upper tract calculus disease. The endo-urological techniques of percutaneous nephrostomy (PCN), lithotripsy (PCNL) and ureteroscopy are essential to manage obstructive complications (urosepsis and renal failure) and provide an alternative treatment for patients unsuitable for ESWL.

Most renal stones are opaque and their fragments pass spontaneously after ESWL. Larger lucent calculi and those that cannot be focused due to an anatomical problem are removed percutaneously. Synchronous PCNL and endoscopic pyelolysis resolve the complication of pelviureteric jucntion obstruction. Larger stones are debulked by PCNL before ESWL. This provides a nephrostomy as an alternative conduit for the passage of the stone fragments and reduces the stone mass for treatment.

Ureteric stones in the abdominal ureter that require treatment are manipulated to the kidney transurethrally and fragmented by ESWL. Those below the bony pelvis are extracted or disintegrated through the ureteroscope, under vision.

Calculus obstruction and urosepsis are resolved by a fine PCN and then treated appropriately by ESWL or endo-urological techniques.

Open surgery is reserved for the removal of non-functioning kidneys or correction of anatomical abnormalities and accounts for less than 5% of procedures in a stone centre.

The Endoscopic Management of Ureteric Calculi

By M. Marberger
Rudolfstiftung, Vienna, Austria

Ureteric calculi may be removed endoscopically via (i) a percutaneous nephrostomy in the retrograde direction, (ii) with the uretero-renoscope via the bladder, or (iii) by a combination of both techniques, *i.e.* pushing the calculus back into the kidney and removing it percutaneously.

Technique (i) is effective for removing calculi wedged in the pelviureteric junction but fails frequently for stones further down the ureter. Technique (ii) is highly successful for smaller calculi regardless of their position, but larger stones cannot be extracted and require intra-ureteric disintegration. Ultrasonic lithotripsy under direct vision with a 2-channel uretero-renoscope has proven effective, but for calculi in the upper third of the ureter technique (iii) is simpler.

In 192 patients with ureteric calculi managed endoscopically, the overall success rate was 84%, with a complication rate of 2% and a mean time of hospitalisation of 4.1 days. The success rate was almost identical for males and females and varied only slightly for stones in the proximal, central or distal third of the ureter.

At follow-up of up to 24 months, only 1 of 24 patients showed sterile grade 1 reflux; there was no evidence of late ureteric stenosis, renal scarring or iatrogenic urinary infection.

The Development of a New Ureteroscope Introducer

By D. R. Webb, J. E. A. Wickham, S. R. Payne and J. M. Fitzpatrick
Meath Hospital, Dublin; Institute of Urology, London; Devonshire Hospital Lithotripter Centre, London, UK

Even after considerable experience, it can still be difficult or impossible easily to introduce the ureteroscope into the lower ureter due to angulation of the ureteric orifice, the submucosal tunnel, the vesico-ureteric junction or prostatomegaly.

Using a ureteric catheter passed through the ureteroscope with a small hump proximal to the tip, the roof of the submucosal tunnel was elevated, facilitating easy insertion of the ureteroscope even without prior dilatation. This prototype was tested successfuly in 10 patients, including 3 males with prostatomegaly.

A purpose-built introducer was developed with a floppy spring-tip that included a memory hump to lift the roof of the submucosal tunnel. This was followed by a semi-rigid guide that can be easily manoeuvred from the proximal end under vision. This device allowed easy introduction of the ureteroscope. The floppy lead easily negotiated the vesico-ureteric junction and the more rigid follower, by decreasing the angle and tortuosity of this segment, greatly assisted the passage of the ureteroscope into the lower ureter.

Ureterolithotripsy in the Dog Ureter

By D. R. Webb and J. M. Fitzpatrick
Urological Department, Meath Hospital; Department of Surgery, Trinity College, Dublin, Ireland

Percutaneous and transurethral access to the ureter have created a new branch of surgery. The ureter is a narrow tube which closely grips calculi and tumours, is not easily distensible and is liable to stricture formation. Experimental results obtained from the kidney or bladder do not necessarily correspond to the ureter for these reasons. To date, experimental urethral stone surgery has been made difficult because insertion of a calculus from the bladder is unlikely to be successful and instruments passed via lower ureterotomies have perforated the upper ureter or been associated with strictures, thus invalidating experimental results.

This paper describes a new method for atraumatic calculus insertion into canine ureters and the results of subsequent ureterolithotripsy by ultrasonic and electrohydraulic probes. Twenty-eight stone destructions were performed. Ultrasonic ureterolithotripsy was found to be safe and effective. Electrohydraulic ureterolithotripsy was also effective but requires caution and experience.

A Whole Urine System for Studying Nucleation, Growth and Aggregation of Calcium Oxalate Crystals

By R. L. Ryall, C. M. Hibberd, B. C. Mazzachi and V. R. Marshall
Flinders Medical Centre, Adelaide, South Australia

The aim of this project was to develop a system for measuring CaOx crystallisation in whole urine and to determine whether undiluted urines from stone formers and normals differed in their responses to a given oxalate load. Twenty-four-hour urine samples were collected from 32 normal men and 50 men who had passed at least one calcium stone within the previous year. After centrifugation and filtration (0.22 µm), aliquots of each urine sample were treated with sodium oxalate to give final exogenous oxalate concentrations of 0–1.5 mM. These were incubated at 37°C for 30 min and the minimum amount of oxalate necessary to induce crystallisation was determined by using a Coulter Counter to estimate the number of crystals in each sample. Once this value was determined for each urine specimen, that amount of oxalate, plus an additional 30 µmol was added dropwise to 100 ml samples of the urine and the growth of precipitated crystal was followed for 90 min using a Coulter Counter to measure increasing crystal volume.

Urines from the stone formers and normals did not differ with respect to the minimum amount of oxalate necessary to induce precipitation. However, when the metastable limits of the urines were expressed as [Ca] × [Ox] total, where total = endogenous + added oxalate, then the product was significantly lower in the stone formers ($P < 0.05$). The groups were not distinguishable with regard to the total volume of crystals precipitated during the incubation period, the rate of crystal growth or crystal size.

CaOx monohydrate (COM) was the principal crystal type in 19 urine samples. In the remainder, classical "envelope" CaOx dihydrate crystals (COD) and aggregates, identical to those found naturally in urine, predominated.

It was concluded that urines from stone formers have less inhibitory activity than those of the normals, but that this may be a result of lower inhibitor concentration.

The Contribution of Bladder Secretions to the Inhibitory Activity of Voided Urine

By K. A. Edyvane, R. L. Ryall and V. R. Marshall
Flinders Medical Centre, Adelaide, South Australia

The soluble glycosaminoglycans (GAGs) are one group of urinary macromolecules which have been shown to account for some of the crystal inhibitory activity in urine and which may protect individuals from stone formation. In this study we postulate that a portion of the observed inhibitory activity of urine is derived from GAGs or other macromolecules from the bladder mucosa.

Saline (0.15 M) bladder washouts were obtained from 31 normal patients undergoing routine cystoscopy. After an initial urine sample was obtained, the bladder was lavaged via the endoscope for 30 s with sterile normal saline using a 50 ml syringe and the washout collected. To account for urinary contamination in the collected washout, a urine control was prepared by diluting the whole urine sample to the same creatinine concentration as the bladder washout. The inhibitory activities of the samples were then measured in a standard seeded crystallisation system.

Microscopic blood contamination ($<0.01\%$) caused an artifactual increase in the inhibition of aggregation in the first nine subjects. In the following 22 subjects, where contamination was excluded by the use of sensitive haemoglobin test strips, no increase in the inhibition of aggregation was seen, whereas crystal growth inhibitory activities were consistently greater in the washouts ($P < 0.01$). This suggests that the bladder is a source of inhibitor(s) of crystal growth and thus questions the use of voided urine in crystal growth studies.

Trace amounts of blood (0.0005%) strongly inhibited crystal aggregation, but not crystal growth over the same range. The potent inhibitory activity of blood could be attributed almost entirely to plasma proteins, with less than 1 µg/ml protein producing marked inhibition. Therefore, microscopic haematuria must be accounted for when examining urinary inhibitory activity.

A Comparison of Risk Factors for Calcium Stone Disease in Male and Female Subjects

By R. L. Ryall, R. M. Harnett, B. C. Massachi, R. D. Mazzachi and V. R. Marshall
Flinders Medical Centre, Adelaide, South Australia

There is a striking disparity in the incidence of calcium urinary stones between the sexes. The object of this study was to ascertain whether this could be attributed to differences in the recognised risk factors for the disease between men and women.

Twenty-four-hour urine samples were collected from 44 normal women, 42 normal men and 32 women and 63 men who had passed a calcium stone or had radiological evidence of new stone formation within the previous year. All subjects were on free diets and the urines were analysed for calcium, oxalate, urate and glycosaminoglycans, and the pH and volume noted. Inhibitory effects on calcium oxalate crystal growth and aggregation were measured using a standart seeded crystallisation system.

The normal women excreted significantly less calcium ($P < 0.0001$; Wilcoxon rank sum test) and urate ($P < 0.0001$) per day than did the normal men, and their urines had a significantly greater inhibitory effect on crystal aggregation ($P < 0.006$). However, the only discernible difference between male and female stone formers was a higher urate excretion by the men ($P = 0.004$).

The female patients exhibited a higher daily output of calcium than did their normal counterparts ($P = 0.003$) and were also older ($P = 0.0005$). Since Ca output in women was proportional to age ($P = 0.004$; Spearman rank order correlation), 17 women from each group were matched for age and their Ca excretion again compared. The Ca output of the stone formers remained significantly higher than that of the normals ($P = 0.005$).

It is concluded that women's relative freedom from calcium stone disease is related to a reduced production of urinary calcium and an increased urinary inhibitory activity which, in turn, are probably related to hormonal status.

The Use of Infrared Photo Coagulation for the Closure of Radial Nephrectomies

By R. G. Grainger, D. R. Webb, P. A. Alken, J. Thuroff and J. M. Fitzpatrick
Urological Department, Meath Hospital, Dublin; Trinity College, Dublin, Ireland; Johannes Gutenberg Universität, Mainz, FRG

Open renal calculus surgery for branched staghorn stones may require multiple parenchymal incisions to obtain complete stone clearance from the calices. Previous work has shown that radial nephrotomies using the doppler ultrasound probe to select avascular nephrotomy sites caused negligible long-term alteration in renal structure and function. Nephrotomy closure by suture may be difficult owing to lack of capsule or soft parenchyma, or sutures may cut out and the nephrotomy bleed. This study was performed to assess the effectiveness of the infrared coagulator in sealing open nephrotomies and the long-term effects on structure and function.

Six radial nephrotomies were made in the left kidney of 10 dogs at open surgery using doppler ultrasound to define avascular planes. The nephrotomies were deepened to full parenchymal thickness, sealed using the photocoagulator, and the wound closed. Assessment was made at 48 h and 6 weeks by bilateral creatine clearance, intravenous urography, vascular corrosive casting and vascular cast angiography.

No significant alteration in function was seen and the nephrotomies healed to a fine scar.

Urinary Incontinence

An Analysis of Incontinence in the General Population

By R. J. Millard
The Prince Henry Hospital, Sydney, New South Wales

Further analysis of the data obtained from a demographic survey of incontinence in the general population has been conducted. The overall incidence of urinary incontinence was 24% but severe or frequent incontinence was found in 6% of the population. Incontinence was rather more common in the lower socio-economic groups and both incidence and severity rose sharply with age and parity. Nocturnal enuresis in childhood doubled the risk of incontinence in adulthood.

In women, pregnancy, four or more children, recurrent infections, diabetes, hysterectomy, the menopause and impaired mobility significantly increased the risk of incontinence. In men the incidence of incontinence rose sharply over 60 years of age. In the elderly of both sexes there was a 40% incidence of incontinence and these findings were confirmed by a survey of 2000 patients in nursing home or geriatric care.

The types of incontinence varied with age. The elderly showed a greater tendency to urge, urge and stress, and dribbling incontinence. Stress incontinence alone rarely occurred over 30 years of age. In men, post-micturition dribbling was extremely common at all ages up to 60 years, when urge incontinence alone became predominant.

Even amongst the severely incontinent only 40% had ever sought treatment or professional help. There is a great need for better education amongst the general population to encourage sufferers to seek the help that is now available.

Experience with Endoscopic Culposuspension

J. S. Jose and A. J. Porter
Royal Adelaide and Calvary Hospitals, Adelaide, South Australia

Fifty-eight cases of stress incontinence treated by endoscopic culposuspension (Stamey procedure) in a 2.5 year period have been reviewed by questionnaire and clinical interview. The operative technique used was that described by Stamey in 1973, with minor modifications.

Of the 54 patients available for study, good results were obtained in 36 (67%), improvement in 10 (18%), while 8 (15%) have remained incontinent.

In the 18 patients with unsatisfactory results, identifiable causes of failure included bladder instability (2), neurogenic bladder (1), sphincteric incompetence (4; 2 were post-traumatic) and psychosis (2). Inadequate technique early in the series accounted for three failures. A tendency to stretch the strict indications for surgery to help the grossly incontinent is reflected in these results. Recurrent incontinence usually became evident within 4 months of surgery.

There have been no serious complications. Two patients required prolonged supra-pubic catheterisation to re-establish normal voiding.

Endoscopic culposuspension can be recommended as a cure for stress incontinence in the stable bladder, particularly when there is no associated cystocele, when previous surgery for stress incontinence has failed, and in the frail and elderly.

The Technique of the Cato-Murray Operation

By A. G. S. Tulloch
Perth, Western Australia

Cato and Murray first described their operation in 1981. It has now become the most popular suprapubic operation in Western Australia for the primary treatment of urinary stress incontinence.

The Cato-Murray operation uses the principle of elevating and stabilising the bladder neck—as in colposuspension. Through a Pfannenstiel incision, the superior surface of the bladder and urethra is mobilised. A single piece of 2 mm Teflon tape, with No. 4 round-bodied Mayo needles mounted at each end, is used. The tape is first passed through the rectus sheath and rectus muscles close to the symphysis pubis in order to suspend the bladder neck from the anterior rectus sheath. Each needle is then passed in turn through the para-urethral tissues lateral to the proximal part of the urethra and adjacent to the bladder. The accurate placing of these tapes is crucial. The abdominal operator and the vaginal operator checks that the tape has not entered the vagina. Each needle is then passed back through the rectus muscle and sheath, the needles removed and the ends of the tape are tied together.

Reference

Cato, R. J. and Murray, A. G. (1981). Teflon tape suspension for the control of stress incontinence. *British Journal of Urology*, **53**, 364-367.

Voiding Difficulties Following Burch Colposuspension

By P. L. Dwyer and S. L. Stanton
Department of Obstetrics and Gynaecology, St George's Hospital, London, UK

Clinical and urodynamic data of 187 women who underwent Burch colposuspension for genuine stress incontinence were studied to determine the incidence and significance of post-operative voiding difficulties. All patients had pre- and post-operative urodynamic investigations and were followed yearly for 1 to 5 years. Seventy-one of 187 patients had a proven voiding difficulty (repeated PFR < 15 ml/s) when assessed urodynamically 3 months after colposuspension. One patient in 5 still had a low flow rate at the end of the follow-up period (mean 2.7 years). There was no evidence of ureteric reflux or upper tract dilatation on videocystourethrography and IVU at 3 months. Recurrent urinary tract infection was a problem in only five patients.

Seventeen patients had an objective voiding difficulty pre-operatively and 14 continued to have this post-operatively: these patients took longer to establish normal micturition ($P<0.05$). The pre-operative peak flow rate was significantly lower ($P<0.01$) in patients who subsequently developed voiding difficulty post-operatively. The symptoms of voiding difficulty were unreliable and of these, a poor urinary stream was found to be the most predictable. No relationship was found between post-operative voiding difficulty and the subjective operative findings of bladder neck elevation and approximation of paravaginal tissues to the ileopectineal ligament. There was no relationship between the time taken to void spontaneously following colposuspension and subsequent voiding difficulty, but detrusor instability was more common post-operatively in this group. There was no relationship between the cure of stress incontinence and the presence of voiding difficulty.

Uroflowmetry is a worthwhile investigation prior to colposuspension, especially when symptoms of voiding difficulty exist beforehand.

Interferential Therapy in the Treatment of Urinary Stress Incontinence

By R. J. Millard
The Prince Henry Hospital, Sydney, New South Wales

Electrostimulation of the pelvic floor is known to be helpful in the treatment of stress incontinence. In theory, interferential therapy should be effective in incontinence because by careful selection of the frequency band it should be possible to stimulate both smooth and striated components of the distal sphincter mechanism.

Sixty-four women with clinically obvious stress incontinence were selected for treatment after full video-urodynamic assessment. Thirty-three patients had had 58 previous unsuccessful surgical procedures.

Patients were given an average of 11 20-min interferential sessions, at a rate of 2 or 3 sessions per week for 4 to 6 weeks. Between sessions patients were instructed to perform pelvic floor exercises at 2- to 4-hourly intervals every day and to monitor the effectiveness of the contractions by their own digital vaginal examination on a daily or weekly basis. Results were assessed at 3 months.

Thirty-three per cent of the patients were cured and 37% were significantly improved by the treatment programme. Patients with unstable bladder function and those who had had previously unsuccessful surgery showed similar 70% response rates. Only 61% of the elderly and 50% of obese patients responded. Patients who were cured remained well for up to 12 months.

Improvement maintained for 12 months suggests that the symptomatic improvement must result from an enduring change in the functional competence of the distal urethral sphincter mechanism.

Subtrigonal Phenol Injection for Female Urge Incontinence. A Follow-up Study and Review of the Role of Second Injections

By R. W. Lloyd-Davies, R. Ewing, E. Palfrey,
M. I. Bultitude and K. E. D. Shuttleworth
St Thomas' Hospital, London, UK

Ewing *et al.* (1982) reported the initial study of this technique from St Thomas' Hospital in 30 female patients with detrusor instability mostly with multiple sclerosis and showed that 76% of all incontinent patients became dry within 1 week of injection.

Fifty-nine patients have now been followed up for up to 5 years and have received a total of 76 injections.

Ninety per cent of multiple sclerosis patients with motor detrusor instability and 66% of those with idiopathic motor instability have achieved a cure of their symptoms. Cure in this situation was defined as:

1. An increase in bladder volume on urodynamic studies of 50% before incontinence.
2. Socially acceptable incontinence.
3. No bypassing of indwelling catheters.

Three major complications, vesicoureteric reflux, vesicovaginal fistula and vesical calculi, have necessitated treatment with a satisfactory outcome.

Further injections have been undertaken because of initial poor response in the early patients and the gradual return of symptoms at 6 months and 2 years. No response in patients with sensory urgency was recorded in this series.

This technique is simple, safe and effective and can greatly improve the quality of life in patients with distressing urinary incontinence.

Reference

Ewing, R., Bultitude, M. I. and Shuttleworth, K. E. D. (1982). Subtrigonal phenol injection for urge incontinence secondary to detrusor instability in females. *British Journal of Urology*, **54**, 689-692.

The Repair Irradiation Fistulae and the Resolution of "Frozen" Pelvis

By R. T. Turner-Warwick
The Middlesex Hospital, London

Vescial fistulae can be broadly classified as "simple" and "complex". The designation "complex" indicates fistulae associated with:

1. Unusually extensive paravesical tissue damage result-

ing from previous surgery, pelvic fracture and gunshot injuries etc.

2. Impaired tissue healing resulting from diabetes, infection or irradiation.
3. Ureteric or sphincter mechanism injury requiring synchronous reconstruction.

A universal abdominoperineal position is generally advisable for all cases. Almost all complex fistulae can be closed in one stage with appropriate use of an interposition omental graft—thus failure to close any fistula calls into question either the choice of procedure or surgical technique.

The so-called "frozen pelvis" resulting from extensive irradiation fibrosis is still generally regarded as inoperable and is usually treated by diversion; nevertheless the essentials for functional reconstruction—the anal and the urethral sphincter mechanisms—are often intact. However, successful reconstruction of a "frozen pelvis" is additionally dependent upon the introduction of a well-vascularised, supple, space-occupying graft to replace the resected hypovital fibrosis and to allow functional movement of the rectum and filling and emptying of the bladder.

The special functional characteristics of the omentum that make it particularly appropriate for this are now well recognised; however, even with full mobilisation of its right gastro-epiploic vascular pedicle, the available bulk is sometimes insufficient to fill the residual pelvic cavity completely after restoration of urinary tract and bowel continuity. For such cases we have developed the alternative principle of a "space-occupying cavity" formed by a bowel segment caeco-vaginoplasty. This principle is also occasionally useful in complex reconstruction/repairs in the male.

Implanted Devices

Artificial Urinary Sphincter Implantation

By G. H. Hirst
Brisbane, Queensland

Between 1980 and 1985, nine American Medical Systems artificial urinary sphincters have been implanted into six patients at the Mater Misericordae Hospital, Brisbane.

Three of the patients had neuropathic bladders caused by a meningomyelocele and the other three had congenital bladder anomalies. Five of the six patients now have satisfactory continence, although 24 open surgical procedures were required to achieve this end.

Of the three patients in the congenital anomalies group, two are completely dry (5 and 21 months) after one implantation only. The other patient had two failed implantations due to erosion of the urethra by the cuff.

All three patients from the neuropathic group have functioning sphincters (after 3 to 22 months). Despite acceptable bladder compliance, low urethral outflow resistance and no residual urine before implantation, all three patients now have mild to moderate urge incontinence even on high dose anticholinergic medication. Urodynamic evaluation confirms that these symptoms are due to the development of bladder instability. Two patients now require intermittent catheterisation for complete bladder emptying.

This experience, although limited, raises the question of whether sphincter implantation alone is appropriate for any neuropathic bladder even with satisfactory preoperative bladder compliance. Bladder augmentation should possibly be considered as a necessary prerequisite for sphincter implantation, even if this subsequently necessitates intermittent catheterisation for bladder emptying.

Local Experience with the Artificial Urinary Sphincter

By R. A. Cartmill
Princess Alexandra Hospital, Brisbane, Queensland

A 3-year experience in the use of the artificial sphincter is reviewed. The difficulties in patient selection as well as the surgical and post-operative problems are emphasised.

Seven males and seven females with an age range of 14 to 78 years underwent the surgery—some after multiple operations.

Two patients required removal of their prosthesis because of urethral erosion. Both of these patients were male with the cuff placed round the bulbous urethra. Ten of the remaining patients have absolute continence. Two female patients are wearing 1 to 2 pads per day.

The artificial sphincter has been shown to be a most successful form of treatment for selected forms of urinary incontinence. Its increasing use is assured, although the decision regarding its use in female patients is not always easily made. It may be that the artificial sphincter should be used earlier in the management of female stress incontinence and therefore avoid the multiple operations required by some of the patients in this series.

The Selection of Patients for Implantation of the Brantley Scott Artificial Urinary Sphincter

By T. P. Stephenson
Cardiff Royal Infirmary, UK

We have implanted artificial sphincters in 100 patients since July 1981. Those with post-prostatectomy incontinence (32) were simple to select. All had gross sphincter weakness incontinence and were urodynamically stable, though reduced compliance up to a pressure of 30 cm of water was not a contraindication. All were implanted with a 50 to 60 cm pressure reservoir. Five had required a

60 to 70 cm pressure reservoir subsequently to control stress incontinence. Two have eroded the urethra after 2 years and required removal and replacement. Erosion is heralded by poor stream and dysuria. The AS 800 should always be used in post-prostatectomy incontinence since it may be de-activated immediately if problems occur.

Stress incontinence is rarely an indication for an artificial urinary sphincter. It is also technically the most difficult. The AS 792 should be used as the AS 800 pump does not fit comfortably in the labium.

In neuropathic dysfunction selection is more difficult and usually involves reconstruction of the whole lower urinary tract, since in most patients there is sphincter incompetence, outflow obstruction at sphincter level and abnormal detrusor behaviour. It is essential to have a motivated, ambulatory patient if major reconstruction is required.

Consequently, only 80 of nearly 500 patients with neuropathic dysfunction have been reconstructed and 52 of these have required either an AS 800 or AS 791/792.

Mentor Inflatable Penile Prosthesis

By S. E. G. Ruthven
Gosford, New South Wales

The Mentor inflatable penile prosthesis consists of two balloons, a pump and a reservoir. The balloons and reservoir are made of a seamless bioreflex material, polyurethane, a new polymer having the physical properties of being inflatable but not distensible.

Eight patients in this series have had the device inserted. The aetiology of their impotence included three who had undergone major pelvic surgery, three with small vessel disease, one diabetic and one patient who had suffered massive pelvic trauma. Follow-up ranged from 1 to 15 months.

All of the prostheses are working to the satisfaction of patients and partners. One patient suffered a tubing kink which was corrected, and another required a dorsal slit for penile oedema. There were no connector or cylinder leaks, no aneurysms and no infections. One patient suffered pain for 6 weeks.

These results are similar to those of overseas experience. Merrell's group have performed 90 insertions of the prosthesis with few mechanical or other complications and an overall success rate of 98%. Compared with an overall success rate of 90% and a mechanical complication rate for the AMS device of between 20 and 40%, the Mentor prosthesis appears to be more reliable.

Penile Prosthesis

By G. S. Reisner
Cabrini Hospital, Melbourne, Victoria

Thirty-nine patients have been treated for impotence by the insertion of a penile prosthesis. Impotence in excess of 12 months' duration was noted in 36 patients. A variety of aetiological factors was encountered. The Jonas prosthesis was used in 31 cases, AMS inflatable in 7 and AMS malleable in 1.

Complications with the Jonas semirigid prosthesis were uncommon and included two cases of flexion of the glans penis and one extrusion. No wire fractures occurred. With the inflatable prosthesis, a hernia of the reservoir required correction and one patient developed a flexion deformity due to lack of early post-operative inflation. No infections occurred in either group.

Most patients and partners were well satisfied with the implant. Natural augmentation of the artificial erection was commonly reported.

Bladder Cancer

The Use of an Animal Model to Gain Insight into Bladder Cancer Therapy

By M. S. Soloway
University of Tennessee Center for the Health Sciences, Memphis, Tennessee, USA

A murine model of bladder cancer, which closely simulates the disease as observed in man, has been used in an effort to answer some of the clinical dilemmas in the management of patients with bladder cancer. The tumour studied in our laboratory is induced by the carcinogen-FANFT. Using an inbred strain the resultant tumours can be transplanted. We have four tumour lines, three of which are transitional cell and the fourth, MBT-409, is a squamous cell carcinoma. Cisplatin (DDP) was identified as an effective chemotherapeutic agent largely by its activity againt the MBT-2 cell line. It is currently the most effective single agent in human bladder cancer. We have compared DDP with numerous platinum analogues against several of the cell lines. DDP remains the most effective platinum analogue.

The additive effect between DDP and radiation therapy (XRT) has been shown in this model. Mice receiving either chemotherapy alone using either DDP or Cyclophosphamide were compared with mice receiving chemotherapy with one of these agents plus either 250 R or 600 R twice a week for 3 weeks. Neither of the chemotherapeutic agents significantly reduced tumour growth, whereas XRT alone provided a 20% increase in their life span compared to the control group. The addition of Cyclophosphamide to XRT did not increase the median survival. The combination of DDP and XRT not only was the most effective regimen but only 22% of the mice in this group developed tumours and these had a significant reduction in tumour growth when compared with untreated controls.

This animal model has also been efficacious for looking at single versus combination intravesical chemotherapy, highlighting the potential for this latter programme. The effect of intravesical chemotherapeutic agents on the normal urothelium was also identified with the use of this murine model.

Distribution of Fibronectin Patterns and HLA-DR +VE Cells in Human Bladder Carcinoma

By R. A. Gardiner, G. J. Seymour, G. M. Strutton and G. Hazan
University of Queensland and Royal Brisbane Hospital, Queensland

Development of techniques of lectin histochemistry and, more specifically, immunochemistry, have permitted superimposition of implied functional information on to the architectural detail provided by conventional histology. In this study, 25 human bladder carcinomas (9 grade I, 9 grade II and 7 grade III) were characterised using monoclonal antibodies for HLA-DR+ and fibronectin. HLA-DR +ve cells include B-lymphocytes and activated T-lymphocytes, macrophages and Langerhans cells. Fibronectin, a component of histological reticulin, is important in cell adhesion, migration and differentiation, and is known in its soluble form to be opsonic in reticulo-endothelial phagocytosis. Fibronectin patterns are known to be disrupted in other tumours *in vivo* and *in vitro*.

Two types of fibronectin patterns were identified. Type A was similar to that seen in "normal" bladders, fibronectin forming continuous bands in the stroma. In type B fibronectin was discontinuous. A continuum seemed to extend from type A to some type B sections in which only specks of fibronectin staining were seen. All grade I tumour sections and 7 and 5 of grade II and grade III, respectively, had type B patterns.

Two types of HLA-DR +ve patterns were also seen. In type Z, HLA-DR +ve cells were present in both tumour and stroma but in type 2 these cells were confined to tumour stroma. Type 2 patterns were identified in 6 and 8 of grade I and II tumours respectively, but the majority (5) of grade III tumours had type 1 pattern.

This form of analysis may provide useful information regarding host/tumour status. However, this preliminary study needs extension both in terms of the numbers and characterisation of the HLA-DR +ve subpopulations before predictive associations can be considered.

Urinary Cytology in the Management of Patients with Bladder Cancer

By M. S. Soloway and W. M. Murphy
University of Tennessee Center for the Health Sciences, Memphis, Tennessee, USA

Urinary cytology is increasingly accepted as a diagnostic tool in the detection and follow-up of patients with bladder cancer. A recent addition to its usefulness is the expertise of cytopathologists in documenting the morphological features of low grade papillary and flat lesions of the bladder epithelium. The cytological features of both papillary TCC and flat urothelial dysplasia have been studied in both experimental systems and clinical situations and this has been applied to the patient setting. Overall, our cytohistological correlation for patients with bladder cancer is 92%. Positive cells reflecting the morphology of the tumour occurred in 62% of patients with grade I TCC and cells suspicious for malignancy were identified in an additional 14%. The correlation for grade II tumours was 77% and 95% for patients with grade III transitional cell carcinoma.

Another important aspect is the cytological alterations associated with intravesical chemotherapeutic agents. We have reported the morphological changes that can occur in the normal urothelium related to intravesical treatment. These changes do not affect the critical measurements of the diagnosis of neoplasm. If cells meeting the criteria for malignancy are identified in the cytological preparation from urine or bladder washing, the cells should be considered cancer rather than cells altered by the drug. The cells of urothelial neoplasms, including low grade TCC, differ morphologically both from normal and reactive and reparative elements and can be detected in cytological samples. These changes are often subtle and require experience and a cautious approach for an accurate interpretation.

A Clinical Experience with Carcinoma *in situ* of the Bladder

By W. Johnson
Royal Melbourne Hospital, Melbourne, Victoria

Experience with 26 patients, 6 with primary and 20 with secondary CIS of the bladder, is reported. Ages ranged from 41 to 78 years; 17 males and 9 females have been followed for 9 to 48 months.

Intravenous cyclophosphamide in 4 patients produced no observable improvement. Adriamycin with phosphate buffer instilled into the bladder in 19 patients produced eight complete responses (CRs), four partial responses (PRs), while seven showed progressive disease. In the follow-up period, however, four CRs relapsed.

Active non-specific immunotherapy, using Pasteur strain of BCG by intravesical instillation, has been used in six patients. There were two CRs and one PR. Invasive tumours developed in three patients.

Urine cytology was valuable both in diagnosis and in assessing response to treatment. A very high incidence of multifocal tumours was apparent. Invasive tumours have occurred despite evidence of regression of CIS following treatment and CIS or tumour recurrences have occurred after complete responses were obtained.

Whilst conservative therapy may be effective in some patients with CIS of the bladder, regular assessment is mandatory. Early cystectomy may be required for failure of response or relapse with CIS or invasive tumours.

Memorial Experience with BCG Therapy

By W. Fair
Memorial Sloane-Kettering Cancer Research Center, New York, USA

In a high risk group of patients with papillary superficial bladder tumours (57% with concurrent flat CIS), prophylactic intravesical BCG as an adjunct to TUR was more effective in reducing the number and rate of tumour recurrences and the need for subsequent cystectomy than was standard TUR alone. With a mean follow-up time of 51 months (range 48-72 months) the overall durable response in the BCG group was approximately 40% in all patients and 65% in the subset of patients with CIS, versus recurrence or progression of disease in all of the control patients within 3 to 6 months. Of the 14 failures in the BCG group, three have required cystectomy (two of these had disease in the prostatic urethra only and a normal bladder); 15 patients required cystectomy in the control group.

A subsequent randomised trial in which responding patients were randomised to monthly maintenance BCG therapy for up to 2 years versus no maintenance showed no difference in the recurrence rate between the two groups.

Intravesical Chemotherapy for Superficial Bladder Cancer

By M. S. Soloway
University of Tennessee, Memphis, USA

Intravesical chemotherapy may be used for either treatment of multifocal, non-resectable superficial bladder cancer or as prophylaxis following complete resection of all evident tumour. In the former circumstance, biopsy to determine grade and stage is performed, but the cytology is likely to remain positive and identifiable areas of tumour remain. This calls for an intensive treatment schedule, *i.e.* weekly for 6 to 8 weeks.

Thio-tepa remains the most widely used agent. All studies have shown that it provides a reduction in tumour incidence or numbers of tumours over time when compared with a non-treated group. Myelosuppression occurs in 18% of patients and 4% of instillations; 30 mg per instillation provides equivalent efficacy to 60 mg. BCG is another effective agent and may act by an immunological response or by creating a local inflammatory reaction. Most studies emphasise its activity in carcinoma *in situ*.

Mitomycin C (MMC) has been used at a dose of 40 mg per 40 ml weekly for 8 weeks when used for treatment. In 70 consecutive patients a 39% complete (CR) and 39% partial response rate was found.

Fifty-six per cent of the patients (39) had failed Thio-tepa and 25 had high grade tumours. The response to therapy did not vary with initial tumour grade or stage. Seven per cent of initial CRs, 15% of PRs and 25% of initial failures developed a muscle invasive tumour in the follow-up period which averaged 28 months for the 70 patients. To date, five patients (7%) have died of bladder cancer.

Synchronous Transurethral Resections of Superficial Bladder Tumours and Prostate

By A. H. Crosthwaite and R. R. Hall
Freeman Hospital, Newcastle upon Tyne, UK

TUR of bladder tumours and the prostate gland at the same time has been considered unwise because of the likelihood of implantation of transitional cell carcinoma in the prostatic fossa. We have reviewed our experience where the procedures had been performed together.

In a 10-year retrospective review of 45 men, 32 had a TUR prostate and TUR superficial tumours of the bladder (Group 1) and 13 had a TUR of superficial urothelial tumour of the bladder neck or prostatic urethra (Group 2).

Nine patients in Group 1 had small superficial recurrences at the bladder neck. There were no recurrences in the prostatic urethra. All four patients in Group 2 with primary prostatic urethral transitional cell carcinoma had recurrences in the prostatic urethra. Two of these later required radiotherapy.

Synchronous resection of benign prostatic hypertrophy and superficial transitional cell carcinoma of the bladder or bladder neck is safe, with no tumour recurrences in the prostatic urethra. Primary transitional cell carcinoma of the prostatic urethra carries a poor prognosis and warrants early radical treatment.

Current Place of Chemotherapy, Radiation Therapy and Cystectomy in the Management of T2 and T3 Bladder Tumours

By W. Fair
Memorial Sloane-Kettering Cancer Research Center, New York, USA

MSKCC experience with various programmes with preoperative irradiation with cystectomy have resulted in the following general conclusions. (1) Pre-operative irradiation does not improve survival in patients with TIS, T1 or T2 lesions treated by cystectomy. (2) Pre-operative irradiation does not improve survival in patients with T4 and N + lesions treated by cystectomy. (3) Pre-operative irradiation approximately doubled the survival rate achieved with cystectomy in patients with T3 lesions. (4) Survival advantage is most pronounced in those patients whose tumours are detectably downstaged by such treatment. (5) 2000 rads in 5 to 7 days appear to produce the same end results in patients with T3 lesions, as do 4000 rads in 4 weeks.

M VAC (methotrexate, vinblastin, adriamycin and cisplatin) administered to patients with transitional cell carcinoma of the urothelial tract induced significant tumour regression in 70% of cases, with complete remission in 40%. The mean duration of response has not yet reached 13 months. These preliminary results indicate M VAC to be an effective regimen for loco-regional and disseminated urothelial tumours with the expectation of inducing objective tumour regression in 53 to 89% of cases.

First-line Intravenous Cisplatin in the Management of Invasive Bladder Cancer

By D. Raghavan, B. Pearson, G. Coorey, P. Duval, M. Rosen, H. Watt, H. Learoyd, D. Arnold and R. Wines
Royal Prince Alfred Hospital, Sydney, New South Wales; Illawarra Urology Unit; and collaborating hospitals

The 5-year survival of patients with deeply invasive bladder cancer is 30 to 50%. To improve the prognosis of patients with high grade, invasive TCC of the bladder, a programme of treatment was initiated in 1981 which incorporated first-line intravenous cisplatin (100 mg/m^2 q 3-weekly ×2) followed by standard definitive treatment (radiotherapy and/or cystectomy), as previously reported. More than 70 patients have been treated, with a mean age of 63.5 years (SD 8.1, median 65, range 29-79) and male:female ratio of 4:1. Eighty per cent had grade III tumours, 82% had T3 to T4 tumours and 50% showed radiological evidence of renal tract obstruction/dilatation or non-function.

At check cystoscopy and restaging after 2 doses of cisplatin, 60% of the first 50 patients treated showed an objective response; after definitive treatment, the response rate increased to 86% (non-invasive staging in the majority). The median duration of follow-up is 23 months (Nov. 1984).

The actuarial survival at 3 years for the first 50 patients was 70%, and disease-free survival 56%. Relapses have been documented in the pelvis alone (20%), bone (14%), nodes (8%), liver (4%), and less frequently in skin, brain and peritoneum. Ten of 15 deaths occurred within 12 months of the start of treatment. In some instances, salvage chemotherapy has secured durable symptomatic and objective remissions.

Systemic Chemotherapy for Metastatic, Locally Advanced, or Adjuvant Use in Bladder Cancer

By M. S. Soloway
University of Tennessee Center for the Health Sciences, Memphis, Tennessee, USA

Cisplatin (DDP) has been the cornerstone for single or combination chemotherapy for advanced bladder cancer. The advent of excellent anti-emetics, both single and in combination, such as Metaclopropamide and Decadron, have greatly alleviated the major side effect of DDP—nausea and vomiting. Used as a single agent, the response rate has ranged from 20 to 35%, with most of these responses being partial and an average duration of response 6 months. The National Bladder Cancer Group found a response rate of 20% and documented that Cyclophosphamide did not contribute when added to cisplatin. More recently, a 3- and 4-drug combination regimen, including DDP, Methotrexate and Velban, has provided response rates above 50% with 20% being complete clinical response.

Cisplatin has been used in an adjuvant setting following pre-operative radiation therapy and cystectomy. Although this was a difficult protocol, with relatively few patients randomised to receive chemotherapy, there was no survival benefit in those patients randomised to receive DDP compared with a non-treated control group.

There is an additive effect between DDP and radiation therapy. In patients who are unsuitable for cystectomy, the combination of DDP with concurrent full-dose radiation therapy has provided a suggested additional benefit when compared with series in which patients received only radiation therapy for equivalent stage T2 to T3 disease. Further trials in the use of this combination seem warranted.

Prostatic Cancer

Objective Tumour Responses to Ketoconazole Therapy with Relapsed Prostatic Cancer

By D. J. Kerle, G. Williams, C. Smith, T. Yeo and S. R. Bloom
Hammersmith Hospital, Royal Postgraduate Medical School, London, UK

The contribution of adrenal androgens to the maintenance and progression of prostatic carcinoma was studied in 20 patients with advanced relapsed disease. The role played by testicular androgens had been negated by prior orchiectomy or concurrent LHRH analogue therapy. Ketoconazole, an anti-fungal agent which inhibits adrenal androgenesis, administered in a dose of 500 mg 8-hourly, resulted in optimal suppression of adrenal androgens. The mean serum androstenedione concentration fell from 8.01 ± 0.84 nMol/l to 1.74 ± 0.39 nMol/l, ($P = 0.001$) and serum testosterone from 1.25 ± 0.14 nMol/l to 0.36 ± 0.06 nMol/l ($P < 0.001$) after 6 months' treatment. There was, however, no significant difference between those receiving 400 mg and 200 mg tds. Androgen suppression resulted in five objective and ten subjective clinical responses as assessed by the British Prostate Group criteria of response.

Ablation of both testicular and adrenal androgens can now be achieved using ketoconazole in combination with orchiectomy or LHRH analogues, but the high incidence of side effects will preclude its use in many patients with prostatic cancer. The concept of "total androgen ablation" as primary therapy in advanced prostatic cancer is suggested as a possible means of improving survival in this common malignancy.

Long-Term Experience of an LHRH Analogue, Zoladex, in Advanced Prostatic Carcinoma

By D. J. Kerle, G. Williams, C. Smith, T. Yeo and S. R. Bloom
Hammersmith Hospital, Royal Postgraduate Medical School, London, UK

Luteinising hormone releasing hormone (LHRH) analogues, superactive agonists of the hypothalamic peptide, inhibit testicular androgen production and result in castrate concentrations of serum testosterone with 21 days of commencing treatment. These analogues are free from side effects and avoid the usual objections to orchiectomy and oestrogen therapy.

The analogue has been evaluated in 40 patients with advanced metastatic prostatic cancer.

The analogue was administered by daily subcutaneous injection of 250 µg to 17 patients who had relapsed or failed to respond to standard hormone therapy. There have been no objective responses but prolonged relief of severe bone pain has been a feature.

Fifteen newly diagnosed patients have used the analogue for a mean period of 14.2 months (range 2-28). At 6 months, three complete, nine partial and two stable responses were documented (British Prostate Group criteria). After 12 months, serum testosterone has risen in four patients, all of whom have subsequently relapsed. This escape from endocrine control initiated conversion of therapy to a continuous release formulation of the drug (depot). Even so, two further patients in this group have escaped endocrine control.

However, Depot Zoladex has also been evaluated in eight patients with advanced disease who had not had previous hormone therapy. After 6 months' treatment, 24-h hormone profiles revealed castrate levels of testosterone in each patient, all of whom remain clinically stable.

The long-term endocrine and clinical results of these studies indicate a specific role for the depot preparation of this agent for the treatment of newly diagnosed prostatic cancer.

Prognostic Criteria for Prostatic Cancer

By P. T. Scardino
Department of Urology, Baylor College of Medicine, Houston, Texas, USA

In order to determine the important features which affect the prognosis of patients with clinically localised prostatic cancer, we performed a multivariate analysis of seven pre-treatment parameters thought to be significant. These included the stage and grade of the primary tumour, the presence of obstructive voiding symptoms, the type of initial biopsy (needle or TUR), the status of the pelvic lymph nodes, and the serum acid and alkaline phosphatase levels. When the interval free of recurrent tumour (local or distant) was used as the endpoint, the statistically significant parameters were stage, grade, obstructive symptoms, nodal status and acid phosphatase level. This type of analysis allows determination of the relative risk of recurrence over any given period of time for each parameter when all other parameters are balanced out. For example, we might ask: all other things being equal, what is the relative risk of recurrence per year of follow-up for patients with positive as opposed to negative pelvic lymph nodes? The results indicated a relative risk of 3.27 for positive nodes, 2.54 for poorly differentiated tumours, 1.71 for an elevated acid phosphatase, 1.40 for obstructive voiding symptoms, and 1.37 for stage B2 or C disease. Hence, the status of the pelvic lymph nodes was the single most powerful prognostic feature of localised prostatic cancer.

The Place of Staging Lymphadenectomy in Prostatic Cancer

By P. T. Scardino
Baylor College of Medicine, Houston, Texas, USA

Pelvic lymph node dissection has now been performed in thousands of patients with apparently localised prostatic cancer. The indications, results and complications of the operation and the prognostic significance of the results are now known.

Using a limited bilateral dissection of the external iliac, obturator and hypogastric nodes, we found that 31% of 475 patients had positive nodes. The incidence was 27% in stage A2, 8% in B1N, 25% in B1, 35% in B2 and 43% in stage C1. In only one-third of these patients were the nodes grossly positive at operation, two-thirds suggesting that a complete dissection is necessary if nodal metastases are to be detected.

The 5-year disease-free survival rate in patients who received no hormonal therapy was 70% if the nodes were negative but only 25% if the nodes were positive ($P < 0.0001$). In order to determine whether there is a subset of patients with positive nodes who have a favourable prognosis, we examined the disease-free survival rate of 37 patients with one single microscopic positive node. At 5 years, 33% of these patients remained disease-free, compared to 17% if multiple nodes were positive and 13% if the nodes were grossly positive. However, by 7 years, 95% of patients in each of these three groups developed recurrence (local or distant). Only 7% of patients with negative nodes have died of prostatic cancer (mean follow-up 64 months), compared with 27% if one single node was positive, 28% if multiple nodes were positive, and 26% if the nodes were grossly positive.

Nodal status is the single most powerful prognostic factor in patients with clinically localised prostatic cancer. The finding of even one single microscopic positive node indicates systemic disease unlikely to be controlled by pelvic lymph node dissection and radiotherapy.

Interstitial Iodine Implantation

By W. Fair
Memorial Sloane-Kettering Cancer Research Center, New York, USA

This is a preliminary analysis of survival and recurrence with the first 402 patients treated at MSKCC between 1970 and 1978, all of whom were at risk for 5 years and 110 at risk for 10 years. The overall survival rate of 5 years was approximately 80% and at 10 years approximately 45%. A highly significant correlation between nodal status, tumour progression and survival was evident. At 5 years 30% of patients with negative nodes had progressed, whereas more than two-thirds of patients with positive nodes had progressed. The effectiveness of interstitial radiation in providing local control is 90% with B1 lesions. For larger lesions (although still confined to the prostate) the local failure rate ranges from 25 to 32%.

Further analysis is necessary to determine whether modifications in surgical and radiation technique and different criteria for case selection, all introduced in 1978, will improve these results.

Excisional Surgery versus Radiotherapy in Prostatic Carcinoma

P. T. Scardino
Baylor College of Medicine, Houston, Texas, USA

Few subjects generate more controversy than the management of localised prostatic cancer. Radiotherapy has become the most common form of treatment in North America. Techniques of radiotherapy include external beam irradiation, iodine seed implantation and gold seed implantation combined with external irradiation. Each has its advantages and disadvantages, but long-term results now indicate that even the best techniques frequently fail to eradicate local tumour. Based on biopsy results, post-treatment rectal examinations and clinical local recurrence, 15 to 45% of clinical stage A and B, and 50 to 60% stage C tumours are not eradicated with radiotherapy. Furthermore, the complication rate remains high for such problems as erectile impotence, which is now being reported in up to 25% of patients after ^{125}I and 79% with external beam therapy.

For these reasons, there has been a resurgence of interest in radical prostatectomy. Long-term disease-free survival appears to be comparable to age-matched controls if the disease is confined to the prostate, and current staging studies such as acid phosphatase, bone scan, transrectal ultrasonography and pelvic lymph node dissection can identify such patients with great accuracy. With the Walsh modified technique, very few patients are incontinent and erectile potency is preserved in 80%.

Current data therefore support the following recommendations:

For stages A2 or B tumours in healthy patients <70 years of age with negative nodes, radical prostatectomy. If life expectancy is short (<10 years), an implant technique. If the patient is a poor surgical risk, external beam therapy.

For stage C, gold seeds plus external beam if the patient is a good surgical risk, or external beam alone if he is not.

For positive nodes or large local tumours, palliative therapy only.

Modified Radical Prostatectomy with Preservation of Potency

By P. T. Scardino
Baylor College of Medicine, Houston, Texas, USA

Based upon the anatomical descriptions of Walsh and Donker, a modification of the standard radical retropubic prostatectomy has been developed which allows preservation of the autonomic nerves responsible for penile erection (Walsh modified radical prostatectomy). Over the past 2 years this operation has been used in more than 25 patients with localised carcinoma of the prostate.

All patients have achieved normal urinary control and in those patients who had normal erectile potency before the operation, erections have returned in 50% by 6 months and in 100% by 12 months after the operation. By using transrectal ultrasonography to identify the anatomical extent of the tumour pre-operatively, we have been able to select appropriate candidates for this operation more accurately than using the standard digital rectal examination. In a series of 16 consecutive patients who had step sectioning of the prostate and pelvic lymph nodes after surgical resection, only one patient had extension into the seminal vesicle (with positive nodes) and a second patient had extension outside the capsule of the prostate, leaving 14 of 16 (88%) with the tumour histologically confined to the prostate gland itself.

This operation, in properly selected patients with localised prostatic cancer, offers a very high probability of cure with minimal morbidity, uniform preservation of normal urinary function and recovery of full sexual function in most patients.

The Significance of Biopsy After Radiotherapy for Prostatic Cancer

By P. T. Scardino
Baylor College of Medicine, Houston, Texas, USA

In order to evaluate the response of prostatic cancer to definitive radiotherapy, we reviewed the results of post-irradiation needle biopsies in patients receiving no other therapy before relapse. A group of 124 patients with clinical stage A2-C1 were treated with pelvic lymphadenectomy, radioactive gold seed implantation and external beam irradiation for a total of 6860 ± 874 rads. They were followed for a mean of 64 months (range 14-175). The disease-free survival rate was 48 ± 11% at 5 years and 31 ± 15% at 10 years.

Biopsy performed 6 to 36 months after the completion of therapy was positive for persistent carcinoma in 43 patients (35%). The incidence of positive biopsy results correlated directly with the size (stage) of the tumour: 22% of B1N, 25% of B1, 29% of A2, 38% of B2, and 50% of C1, but there was no correlation with grade. Biopsy results were positive in 71% if a rectal examination performed at the same time was considered suspicious for cancer, and in 19% if the rectal examination was considered normal.

If the biopsy result was positive, 65% of the patients developed recurrent tumour (47% local recurrence ± distant metastases, 51% distant metastases ± local recurrence). But if the biopsy result was negative, only 31% recurred (14% local, 30% distant). On an actuarial basis, local recurrence of tumour developed in 82% of patients with a positive biopsy compared with only 32% with a negative biopsy at 10 years ($P<0.0006$).

These results indicate that a needle biopsy of the prostate performed a sufficient time after radiotherapy is an accurate index of the success of therapy and will allow the physician to detect treatment failure early, when a second chance at definitive therapy is still possible.

The Adverse Effect of TUR in Carcinoma of the Prostate

By P. T. Scardino
Baylor College of Medicine, Houston, Texas, USA

Several recent reports suggest that transurethral resection (TUR) of localised prostatic cancer may cause early dissemination of the tumour. It seems logical that tumour cells may be disrupted by the resection, be forced into venous sinuses by elevated intravesical pressures during the resection and result in haematogenous dissemination of malignant cells.

To evaluate the effect of TUR in our own patients, we determined the rate of development of distant metastases over time in a group of 222 clinical stage B and C patients who were treated with pelvic lymph node dissection, radioactive gold seed implantation and external beam irradiation. No patient received hormonal therapy unless the tumour recurred. The initial biopsy was by needle biopsy in 161 (73%) and by TUR in 61 (27%).

Metastases developed significantly more rapidly in the TUR group. Even when subsets of patients were compared within each stage and grade, those who had a TUR appeared to do significantly worse than those who had a needle biopsy. But the most powerful prognostic factor in patients with clinically localised prostatic cancer is the status of the pelvic lymph nodes. When the TUR group was compared with the needle biopsy group, the incidence of positive nodes was almost twice as high within the group as a whole and within every subgroup. When the rate of distant metastases was compared within the group of patients with proven negative nodes, however, there was no longer any difference.

Another important prognostic feature, particularly relevant to the question of an adverse impact of a TUR, is the presence or absence of obstructive voiding symptoms. Those with such symptoms have a substantially poorer prognosis, but within the group of patients with obstructive voiding symptoms there was no difference in prognosis whether the patient had had a needle biopsy or a TUR.

Contrary to other reports in which neither the nodal status nor the presence of obstructive symptoms were known, our data show that a TUR is not associated with early dissemination of prostatic cancer. Reports to the contrary have not taken into account the most important prognostic features of the disease.

Newer Agents for Androgen Deprivation in Prostate Cancer and the Current Status of Chemotherapy for Prostate Cancer

By M. S. Soloway
University of Tennessee Center for the Health Sciences, Memphis, Tennessee, USA

Although there have been no major advances in the use of chemotherapy for treatment of advanced prostate cancer, there are now alternatives to diethylstilboestrol (DES) or orchiectomy for androgen deprivation. At least two LH-RH analogues—Buserelin and Leuprolide—provide sustained androgen deprivation as long as the patient takes the drug. The initial rise in LH when beginning therapy results in transient increase in testosterone. By 1 month, castrate levels of testosterone are evident. The primary advantage of these subcutaneous or intranasal drugs are a reduction in the side effects related to oestrogen or the psychological impact required by bilateral orchiectomy. A recently concluded randomised trial comparing Leuprolide with DES, 3 mg daily, indicated an equivalent response rate with a reduction in cardiovascular side effects in the group receiving Leuprolide, 1 mg s.c. daily.

The National Prostatic Cancer Project (NPCP) has continued to treat patients with newly diagnosed D2 disease as well as patients who have failed hormonal therapy with single and combination chemotherapy. Recently completed trials indicate moderate activity with Methotrexate. Cisplatin has shown less efficiency and greater side effects. Ongoing trials include cisplatin + 5-Fluorouracil + cyclophosphamide and the combination of cyclophosphamide and Adriamycin.

Recently completed trials for patients with newly diagnosed metastatic disease on the use of cyclophosphamide or the combination of cyclophosphamide and 5-Fluorouracil plus DES show no survival benefit when compared with DES or orchiectomy.

Aminoglutethimide in the Management of Advanced Hormone-Resistant Prostatic Cancer

By D. Raghavan, P. Harnett, B. Pearson,
I. Caterson, G. J. Coorey, J. Rogers, A. Coates and
J. Boulas
Royal Prince Alfred Hospital, Sydney, New South
Wales

The treatment of patients with recurrent prostatic cancer (CAP) after first-line hormonal manipulation remains a difficult problem. In most published series, the objective response rates (NPCP criteria) with further hormonal or cytotoxic agents are less than 20% and usually of short duration.

We report our experience with aminoglutethimide (AG), an inhibitor of adrenal androgenic steroids. In an ongoing study, 30 patients have been treated with AG (250 mg (qid) and cortisone acetate (25 mg mane, 12.5 mg nocte—a standard replacement dose). The mean age of the patients was 70.2 years (range 54-81). All patients had bone metastases on X-ray and/or radionuclide bone scan; other sites of disease included liver, lungs and abdominal lymph nodes. Seventy-five per cent of the patients had undergone bilateral orchiectomy.

Patients were staged by examination, biochemical screen, assay of prostatic acid phosphatase, gonadotropic hormones, prolactin and androgenic steroids. Tumour measurements included clinical assessment, X-rays, serial bone scans and CAT scans as indicated. Investigations were repeated at regular intervals.

The toxicity of the drug was substantial and included depression (25%), skin rash (16%), postural hypotension (11%) and abnormal liver function tests (7%). Objective responses were noted in 10% of patients and symptomatic improvement in a further 25%; these responses were sustained between 3 and 12 months. In view of the paucity of therapeutic options, AG may have a role in the secondary treatment of carcinoma of prostate.

Keith Kirkland Prize Presentation

* indicates prizewinner

*An Investigation into the Side Effects of Oestrogen Therapy for Advanced Carcinoma of the Prostate

By B. Blyth, C. U. McRae, E. Espiner and
G. Nicholls
Christchurch Hospital, Christchurch, New Zealand

A prospective study was performed to establish the mechanism of salt and water retention in elderly males undergoing oestrogen therapy, in an attempt to predict those liable to encounter problems.

Six patients satisfied entry criteria and following diagnosis were admitted for metabolic studies prior to and after commencement of stilboestrol 3 mg daily, while on fixed sodium intake. Assessments continued over a 3-month period.

Five patients completed the protocol; the sixth died of progressive disease. Serial testosterone and SHBG confirmed patient compliance. Significant findings were a rise in plasma volume, detectable early, with increases in plasma renin activity and angiotensin II. There were significant falls in the postural increments normally seen with plasma renin, angiotensin II and aldosterone. Parameters that did not change significantly were blood pressure, weight, end-diastolic volume and ejection fractions, aldosterone, antidiuretic hormone and plasma catecholamines. There was no evidence of sodium retention while on sodium restriction.

This study provides evidence of plasma volume expansion as a side effect of oestrogen detected in those with no history of cardiac disease and appears to be mediated via the renin-angiotensin system.

Site-Specific Effects on the Differentiation of a Human Germ Cell Tumour Xenograft in Nude Mice

By D. R. Eisinger, P. Gregory, P. Russell,
C. van Haaften-Day, B. S. Pearson and
D. Raghavan
Urological Cancer Research Unit, Royal Prince Alfred
Hospital, Sydney, New South Wales

The metastases of human germ cell tumours may exhibit histological differences from the primary lesion. This study was undertaken to investigate the effects of site of growth on the differentiation of a human germ cell tumour xenograft in nude mice.

A stable well-characterised human yolk sac tumour xenograft, HX112, was serially transplanted through four passages into skin, liver, kidney and spleen in BALB/c nu/nu mice. A two-stage intraperitoneal anaesthetic (fentanyl/droperidol/scopolamine; chloral hydrate/pentobarbitone) was developed to enable major surgery to be safely undertaken in these animals. Tumours were passaged at a diameter of 1 to 2 cm. The xenografts were examined by light and electron microscopy. Flow cytometry was performed on some tumours.

There was considerable morphological variation between tumours from each given site, but no consistent pattern of site-specific histological or ultrastructural differentiation was observed. No consistent pattern of evolution of flow cytometric characteristics was apparent. The use of a site-specific implantation technique may provide a valuable tool for the study of growth, differentiation and treatment sensitivity of heterogeneous tumour cell populations.

Symptomatology and Uroflowmetry in Prostatism

By M. R. Fraundorfer
Dunedin Hospital, Dunedin, New Zealand

A study was conducted to determine how well presenting symptoms of prostatism (either singly or in various combinations) predicted true outflow obstruction as determined by voiding flowmetry.

The 150 patients evaluated were all referred by family physicians with a provisional diagnosis of prostatism and at the time of the initial examination a questionnaire was administered and flowmetry measurements recorded.

Peak and average flow rates were converted to standard deviation units using nomograms prepared by Siroky *et al.* Patients whose flows were less than 1.65 standard deviations from the mean were considered obstructed.

With these data, the predictive value, sensitivity and specificity of six symptoms were obtained. In descending order of value for predicting urinary obstruction these were: hesitancy, nocturnal or full bladder hesitancy, poor stream, post-micturition dribble, urgency and nocturia.

Nocturia was considered to be the most troublesome symptom by 39% of the group, followed by poor stream in 23%.

Hypothermia During Endoscopic Prostatectomy

P. S. Heathcote and P. M. Dyer
Princess Alexandra Hospital, Brisbane, Queensland

This prospective study assessed the effect of space blanket body insulation and warmed 1.5% glycine irrigations on decreasing patient heat loss during endoscopic prostatectomy under spinal anaesthesia. Sublingual temperatures were measures during and for 6 h after operation in 94 patients assigned to one of four groups:

1. Controls—25 patients.
2. With space blankets only—24 patients.
3. With warmed irrigations only—22 patients.
4. With both space blankets and warmed irrigations—23 patients.

Room temperature glycine was 21.5°C and incubator warmed glycine bags were 33.1°C. There was no significant difference between groups for patient age and weight and resection time and weight, and volume of irrigation used.

The control group experienced the greatest mean temperature drop of 1.3°C (0.4-4.1). Using space blanket insulation and warmed irrigations together achieved a highly significant ($P < 0.001$) decrease in temperature drop to 0.8°C (0-2.3), while the incidence of shivering fell from the 52% of the control group to 4%.

Mean blood losses were 140 ml in 37 resections using room temperature glycine and 125 ml in 38 resections using warmed glycine.

Space blanket patient insulation and warmed irrigations significantly decrease heat loss during endoscopic prostatectomy, improving patient comfort without increasing intra-operative blood loss.

The Effect of Intravesical Heparin on Urinary Tract Infections in the Paraplegic Cat Model

P. H. G. Mortensen, H. N. Fenster, B. Robinson, P. J. Moloney and R. W. J. Ford
St. Vincent's Hospital, Melbourne, Australia, and Vancouver, Canada

Recent experimental work has shown a protective function of heparin and other semisynthetic glycosaminoglycans in preventing bacterial adherence to bladder mucosa.

We investigated whether heparin might be of use in preventing the common occurrence of urinary tract infections in the spinal cord injury patient with indwelling or intermittent catheter.

An experimental spinal cord injury cat model was used. Twenty-one cats were studied comparing intravesical heparin and saline on the rate of significant bacteriuria. The animals, after receiving a paraplegic injury, were managed with an indwelling suprapubic catheter for 14 days. They received a daily intravesical instillation of either 1000 units of heparin or normal saline.

There was no significant difference in rate or day of appearance of significant bacteriuria between the two groups.

Patch Grafting of Upper Ureter in Dogs Using Lyophilised Dura Mater

P. L. Royce
Royal Melbourne Hospital, Victoria

This project was conceived to determine whether lyophilised human dura mater (Lyodura) would be a suitable material for grafting in the upper urinary tract. This procedure has become feasible owing to the development of a thinner form of Lyodura, suitable for such grafting.

Six kidneys in three dogs were used in the project. In each renal unit an upper ureterotomy was made and an elliptical patch of Lyodura, 1.5 cm × 0.5 cm, was sutured into the ureteric defect with continuous 4/0 chromic catgut. A 5 F ureteric vinyl stent was used, together with a corrugated rubber drain tube to the operative site. Ipsilateral nephro-ureterectomy was performed at either 2 or 3 months post-operatively, at which time the contralateral upper ureter was grafted. Following a further time interval of either 1 or 2 months, the dog was sacrificed and the solitary kidney and ureter removed for examination.

In three of the six grafts there was no radiographic evidence of hydronephrosis. One graft was associated with persistent hydronephrosis; in another, hydronephrosis resolved after 10 weeks. One dog died following grafting of a solitary left kidney due to renal infarction. Four of five available grafts were satisfactory.

Histological examination showed almost complete resorption of the Lyodura, with replacement by connective tissue and smooth muscle by 14 weeks. The ureteric lumen had been re-epithelialised with transitional epithelium by 5 weeks.

Lyodura is a satisfactory material for grafting the upper ureter in the dog.

Sexual Dysfunction Following Surgery for Rectal Carcinoma: a Prospective Study

By G. Watters, C. Roberts, P. Maher, E. Bokey and P. Chapuis
Concord Hospital, Sydney, New South Wales

The aim of this study was to assess accurately the incidence of organic post-operative sexual dysfunction following surgery for rectal carcinoma by assessing the sexual function of patients prior to and 3 months following surgery. Patients were assessed with a sexual history, physical examination, serum hormone levels (testosterone, FSH, LH and prolactin), penile doppler pressure studies and nocturnal penile tumescence monitoring.

Twenty-seven male patients aged less than 75 years, with a rectal adenocarcinoma less than 18 cm from the anal verge and confined to the bowel wall, participated in the study. Eight patients were impotent prior to surgery and were not reassessed. Three patients refused follow-up and a further two patients defaulted.

Fourteen patients were potent prior to surgery and available for review. One patient had improved sexual function following surgery. One patient was unable to ejaculate, while a further three noticed a decrease in their libido but were still potent. Nine patients were rendered organically impotent by surgery. There was no relationship between the patients' ages or stages of tumour and the incidence of impotence. Patients with tumour less than 10 cm from the anal verge were found to have a significantly higher rate of impotence than those with tumour between 10 and 17 cm.

All six patients who were treated with abdominoperineal resection became impotent compared with three of the eight who were treated with an anterior resection.

Miscellaneous

Sexual Dysfunction After Prostatectomy—Is the Urologist Guilty?

J. W. Bolt and V. R. Marshall
The Queen Elizabeth Hospital and Flinders Medical Centre, Adelaide, South Australia

One of the major and disconcerting complications of prostatectomy is impotence. Several studies have reported only a small reduction in potency rates following prostatectomy, but these studies have failed to examine the effect of surgery *per se* on a group of men in whom one could expect a significant incidence of reduced potency. In order to rectify this defect a prospective study was undertaken to assess the effect of TURP and abdominal surgery on two age-matched populations. In all cases potency and ejaculatory function and frequency of intercourse were assessed pre- and post-operatively. Potency was retained in 88% of the men undergoing prostatectomy and in all of the men undergoing general surgical procedures ($P<0.01$). Of those men who indicated that they were capable of having sexual intercourse prior to operation, 88% were unaffected by prostatectomy. In the general surgical group, 97% were unaffected. Thus it would appear that TURP does have a significant effect on sexual function which cannot be accounted for by the stress of surgery or the age of the population undergoing operation.

The Ureteroscopic Management of Tumours in the Pelvis and Ureter

By W. Fair
Memorial Sloane-Kettering Cancer Research Center, New York, USA

Diagnostic ureteroscopy was attempted in 59 patients with symptoms or signs suggestive of upper tract urothelial tumours. The ureteroscopic procedure was successful in 54 patients (92%) and unsuccessful in 5 (8%).

Twenty-seven urothelial tumours were diagnosed, one metastatic squamous cell carcinoma, three uric acid calculi, one patient with bleeding localised to the lower pole of the kidney, and 22 patients had no abnormality in the ureter or renal pelvis. Of the 27 patients with urothelial tumours, 16 were selected for primary endoscopic management. Of these 14 had localised, low grade ureteric tumours and two patients had high grade renal pelvic tumours in solitary kidneys. Following biopsy, these patients were all treated primarily by ureteroscopic resection or fulguration. Follow-up was done at intervals of 2 to 3 months.

Forty-seven surveillance procedures have been performed in these patients with an average follow-up period of 16 months; 14 low grade recurrences have been diagnosed and treated in 5 patients. One patient died of a myocardial infarction; the remaining 15 are alive with no evidence of tumour dissemination.

Assessment of the Level of Injury of Ruptured Urethra

By D. I. M. Moss
Ballarat, Victoria

A technique has previously been presented demonstrating primary perineal repair of rupture of the membranous urethra associated with pelvic fracture, with excellent results from the point of view of lack of subsequent stricture and preservation of potency. The current study was a retrospective review of 43 cases of urethral rupture, in an endeavour to establish the level of injury, to see whether primary perineal anastomosis would be feasible in all cases.

Original retrograde urethrograms were available in 18 cases for review and in all of these there was perineal extravasation, three extending from the perineum up to within the pelvis. In three cases the verumontanum was visible and the leak identifiable 1 to 2 cm below it.

Four patients were urethroscoped and all showed an injury a few centimetres distal to the verumontanum. In 29 cases the level of the initial injury was unidentifiable (treated by catheter alone, catheter realignment or suprapubic cystostomy alone). A further 10 patients were treated by primary perineal repair, in each case the level of injury being 2 cm distal to the verumontanum, and direct anastomosis was performed from below.

The level of the subsequent stricture was assessed in 30 cases where films were available. In 21 of these an irregularity or established stricture was within 1 to 2 cm below the verumontanum and in no cases higher than this. Urethroscopy was performed during the treatment of stricture in 16 cases, 14 of which showed a stricture 1 to 2 cm distal to the verumontanum.

Post mortem studies were performed by surgically dividing the urethra at various levels and performing retrograde urethrograms. Perineal extravasation occurs where division is below the urogenital diaphragm, 1 to 2 cm below the prostate. Division of the urethra above the diaphragm leads to retropubic and pelvic extravasation, not corresponding to the clinical studies.

Immunohistochemical Analysis of the Human Bladder

By R. A. Gardiner, G. J. Seymour, G. M. Strutton and G. Hazan
University of Queensland and Royal Brisbane Hospital, Queensland

In the urinary tract, despite close scrutiny of urothelial cell antigen status, little attention has been paid to accompanying lymphocyte and macrophage populations. The present study was undertaken to identify the various T-cell and macrophage subpopulations and to determine the pattern and distribution of fibronectin in the human bladder.

Bladder wall biopsies (3 open; 3 closed) were obtained from six patients (4 males and 2 females) aged 34 to 78 years who had sterile urine and normal urinary cytology and in whom bladders appeared normal cystoscopically. Bladder wall biopsies taken immediately adjacent to those obtained for immunohistochemical studies appeared normal when stained by haematoxylin and eosin and examined using light microscopy.

Urothelial cells were HLA-DR −ve, acid phosphatase (AcP) +ve and adenine triphosphatase (ATPase) +ve. All lymphocytes in this layer were of the T8 +ve suppressor/cytotoxic subgroup and dendritic cells with an identical phenotype to Langerhans cells (T6 +ve, HLA-DR +ve and ATPase +ve) were seen. In the lamina propria, most lymphocytes were T8 +ve with some helper/inducer T4 +ve cells also being present. An occasional NK cell (Leu 7 +ve) and Langerhans cell (T6 +ve) were identified and large macrophage cells with a common phenotype to antigen presenting ID cells (T6 −ve, HLA-DR +ve, AcP −ve and ATPase +ve) were noted. Fibronectin staining was dense in the vicinity of basement membranes, merging to form fine interconnecting latticework-like structures elsewhere in the lamina propria.

These results are consistent with the concept of the urothelial surface being an integral component of the mucosal immune system, and are intended to serve as a useful reference for immunohistochemical studies of pathological conditions of the bladder.

Successful Surgical Separation of Omphalo-Pubo-Perineopagus Twins

By D. D. Arnold and A. W. Middleton
Royal Alexandra Hospital for Children, Sydney, New South Wales

Conjoined twins occur once in 50 to 100,000 pregnancies; half of them die within a day or two. The Sydney twins (1983) were joined from common umbilicus to perineum; the pubic symphyses were absent and the corresponding pubic bones were firmly united. Each had anorectal agenesis and there was a single phallus with one meatus to conduct the products of two urinary and two gastrointestinal tracts.

Separation was carried out on the third day of extrauterine life. The common pubic bones on each side were divided first to afford access to the abdomen. A single colon entered the base of the duplex bladder; the latter had two bladder necks and two posterior urethrae but only a single distal urethra. The two small bowels had a Y-junction at the point where a Meckel's diverticulum was found; the common ileum then entered a single caecum which had two appendices. Allocation of the single colon and single penis (and single set of corpora cavernosa) was made on the basis of blood supply.

Chromosome studies showed the twins to be XY. One was designated female and gonadectomy was carried out on that individual. Construction of a vagina was deferred. One twin has a colostomy and the other an ileostomy. Both are thriving 16 months after separation.

The Treatment of Chronic Pseudomonas Infection by Ciprofloxacin in Patients with Anatomically and/or Functionally Abnormal Urinary Tracts

By T. P. Stephenson and E. Brown
Department of Bacteriology and Urology, Cardiff Royal Infirmary, UK

Chronic *Pseudomonas* infection has generally been considered to be a harmless resident in patients with surface diversions and is a common finding in the anatomically or functionally abnormal urinary tracts. It may, however, be the cause of systemic upset and impaired renal function, especially in patients who have been undiverted.

Thirteen such patients with chronic *Pseudomonas aeruginosa* infection have been treated with a 2-week course of Ciprofloxacin.

Twelve patients had sterile urine at the end of treatment but in four patients the organism returned still sensitive to the drug.

In eight cases the urine had remained sterile at least 8 weeks after treatment had been completed. In one patient the organism developed resistance during therapy.

The preliminary study suggests that this oral compound represents a major advance in the treatment of *Pseudomonas* infection in the abnormal urinary tract.

Early Experience with Kock Continent Ileal Reservoir

By C. U. McRae
Christchurch, New Zealand

Continent ileal reservoir urinary diversion as described by Kock (1982) has been carried out in eight patients aged between 5 and 73 years. Indications included carcinoma bladder, intractable incontinence, bladder exstrophy and spina bifida.

Two patients died during follow-up from cardiovascular causes unrelated to the urinary diversion; the remainder have been followed up between 2 and 14 months.

Function of the reservoir has been excellent, allowing patients to empty by intermittent catheterisation 4 to 5 times per day but not requiring emptying at night. Continence has been excellent in all cases but three outlets have required minor revisions due to difficulties in catheterising when the reservoir was full. Functional reservoir capacity has been between 300 and 1000ml. Renal function has shown no change during follow-up and radiology has not indicated any change in upper tracts. In spite of theoretical absorption from the reservoir, no metabolic abnormalities have been found and clinically significant urinary infections have occurred on only a few occasions.

In spite of the operative time and complexity it is considered that this form of diversion offers sufficient advantages in patient acceptability to recommend further clinical use.

Phase II Study of Flutamide in Advanced Prostate Cancer

By G. Sarfaty and S. Alder
Prince of Wales Hospital, Sydney, New South Wales

It is well established that 70 to 80% of prostate cancers will respond to hormonal therapy, but complications and side effects from oestrogens have limited their effectiveness. In recent years, several new forms of systemic therapy have become available. These include anti-androgens, LHRH analogues and enzyme inhibitors such as aminoglutethimide and ketoconazole and hormone cytotoxic conjugates.

A phase II study is in progress of the non-steroidal anti-androgen flutamide in patients with progressive metastatic prostate cancer. Patients eligible for the trial have failed prior hormonal therapy, developed complications or have pre-existing cardiovascular disease contraindicating oestrogens.

To date 32 patients have entered the study and 20 have been analysed. The overall response rate is 50% (10/20). The median time to relapse is 52 weeks. The response rate in patients who had received prior hormone therapy is 38% (6/16).

There has been no toxicity from flutamide in the cardiovascular, hepatic, gastrointestinal, haemopoietic or central nervous system. Mild gynaecomastia or breast tenderness occurred inconstantly. Patients who respond to flutamide have a significantly increased median survival of 64 weeks compared with 10 weeks in patients not responding.

British Journal of Urology (1986), **58**, 95-96

AUTHORS' FOLLOW-UP

Interstitial Cystitis: Possible Cause and Clinical Study of Sodium Cromoglycate

L. EDWARDS, T. E. BUCKNALL and CAROL MAKIN

Department of Urology, Westminster Hospital, London

In our earlier study (Rosin *et al.*, 1979) we investigated 20 histological proven cases of interstitial cystitis in an attempt to find evidence of a possible auto-immune mechanism in its aetiology.

The disease has many features of an auto-immune phenomenon (*e.g.* the apparent absence of a precipitating factor, and phases of exacerbation and remission) and our retrospective investigations indicated that it probably was an auto-immune disease.

Since then we have developed a hypothesis regarding its aetiology. In the first instance, sepsis or trauma causes injury to the bladder, with the cellular destruction leading to the release or alteration of an antigen which reacts with immune-competent cells which may produce antibody. This in turn could cause more bladder damage and fibrosis. Injury, inflammation and fibrosis are parts of a self-perpetuating process (Fig.).

Experiments with rats suggested that sodium cromoglycate (Intal, Fisons) protected bladder mucosa from the effects of known irritants (Edwards *et al.*, 1978). At the time of our initial report we had not used sodium cromoglycate in the treatment of interstitial cystitis, but it has now been used in nine female patients, with satisfactory results in six.

These patients' intractable symptoms were sufficiently severe for us to consider augmentation cystoplasty or diversion. Informed consent was obtained and the following investigations made: full blood count, urea, electrolytes, liver function studies, chest X-ray, electrocardiography and urine microbiology. These tests were repeated every 3

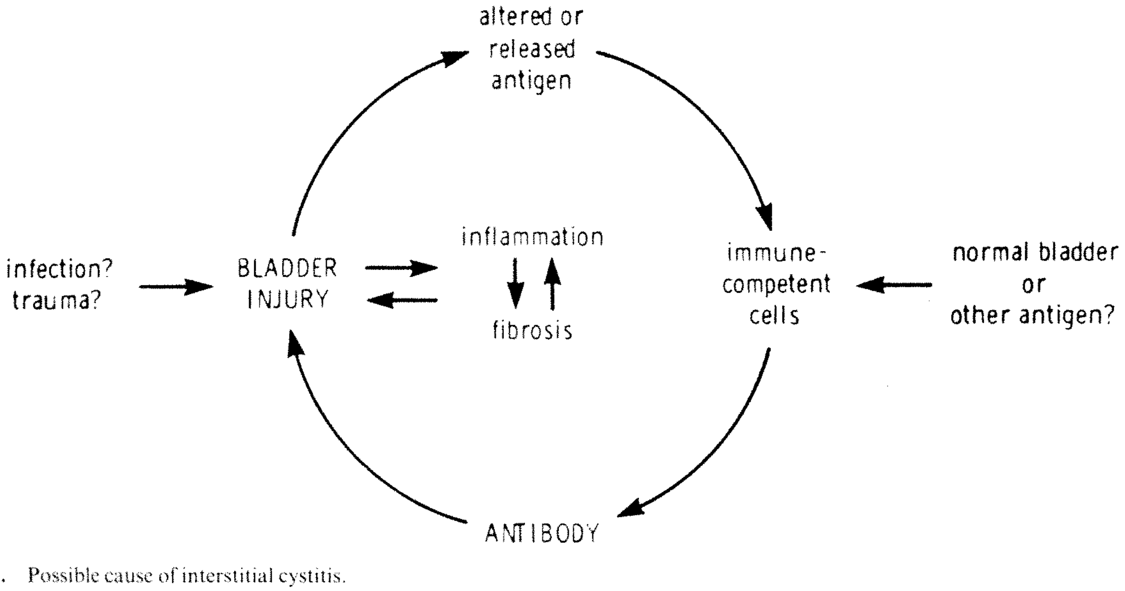

Fig. Possible cause of interstitial cystitis.

days. Cystoscopy was omitted since each patient had been cystoscoped between 6 and 12 weeks previously. The patient was catheterised, the bladder drained and 100 ml of a 4% sodium cromoglycate solution instilled. The catheter was removed and the solution retained for at least 1 h. These painless instillations continued for 12 days. In no case did urinary tract infection develop and all base-line investigations remained stable.

Two patients reported complete resolution of their symptoms. Two years later one remains symptom-free and the other requires regular cystodistension.

Four patients reported a decrease in the severity of symptoms. All are still controlled by "passive" cystodistension, carried out by 5-min stretching with a hydrostatic pressure head of 60 cm.

Three patients derived no benefit. One subsequently underwent "active" bladder distension as described by Helmstein (1972), reverting to "passive" distension. The other two had a caecocystoplasty.

Our clinical results are less promising than we had hoped. Nevertheless, six of the nine patients improved to the extent that more radical procedures were not required, although regular cystodistension continues. We continue to use sodium cromoglycate in patients with intractable symptoms and feel that it has a definite role to play in the management of this distressing condition.

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Requests for reprints to: L. Edwards, Department of Urology, Westminster Hospital, Dean Ryle Street, London SW1P 2AP.

British Journal of Urology (1986), **58**, 97–107

Case Reports

A Vas Aberrans Torsion

J. J. BALLESTEROS SAMPOL, A. MUNNE and A. BOSCH, *Department of Urology, Hospital Ntra. Sra. de la Esperanza, Barcelona, Spain*

Torsion of a "vas aberrans" is an exceptionally rare form of torsion of the testicular appendages. In 1939 Randall reported two such cases and in 1970 Skoglund *et al.* reviewed the literature and found another case described by Cywes in 1966.

Case Report

An 8-year-old child, while playing, developed acute pain in the left scrotal area with progressive enlargement of the scrotum. Three hours later he was seen in this department, where examination revealed enlargement of the scrotum, tenderness, a positive Prehn's sign and negative transillumination. Torsion of the testicle was diagnosed and he was taken to theatre, where a smooth, spherical, dark red mass measuring 35 × 28 × 25 mm was found. It was joined to the tail of the epididymis by a fully twisted pedicle (Fig. 1). The mass was resected at the level of the epididymis and found to be filled under tension with blood-stained material. Its walls were 1 to 3 mm thick and microscopic examination showed them to consist of lax fibrous tissue with extremely congested vessels. They were lined by a single cylindrical epithelium (Fig. 2). Haemorrhagic infiltration of the wall and necrosis had occurred in some areas.

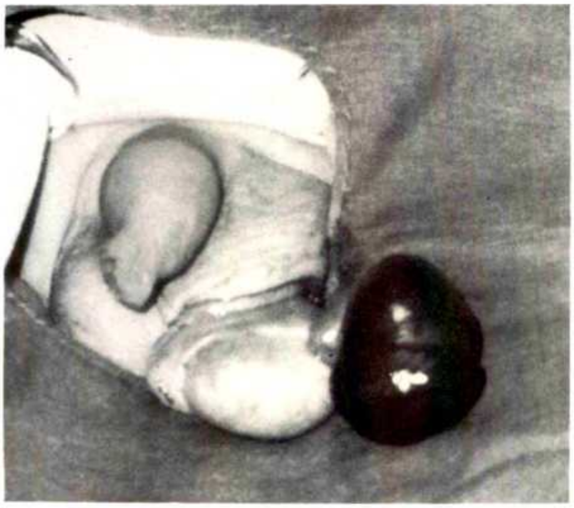

Fig. 1 Operative area.

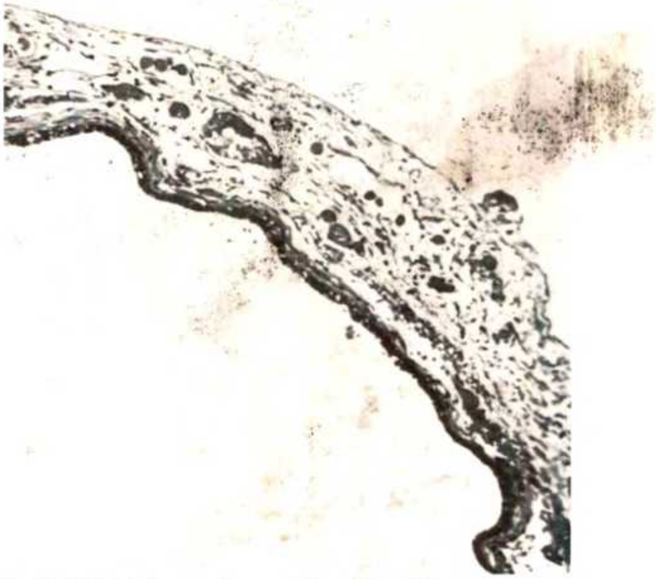

Fig. 2 Wall of the vas aberrans (H and E × 100).

Comment

This is the fourth reported case of vas aberrans torsion. Its exceptional size suggested testicular torsion. In such cases surgery is the best form of treatment.

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Requests for reprints to: J. J. Ballesteros Sampol, Av. de Roma, 101, 7º, 3ª, Barcelona 29, Spain.

Left Nephroureteric Obstruction due to Carcinoma of the Pancreatic Tail

S. EISENKRAFT, P. JONAS and M. MANI, *Department of Urology, Chaim Sheba Medical Center and Sackler School of Medicine, Tel Aviv, Israel*

Pancreatic carcinoma is a rare cause of ureteric obstruction. The diagnosis is made by exploration or after autopsy.

Case Report

A 52-year-old man was admitted with left flank pain. An excretory urogram revealed non-function of the left kidney. No masses were palpable and the remainder of the physical examination was normal. Blood urea nitrogen (BUN) and electrolytes were normal, as were bilirubin and prothrombin time. Glucose was 142 mg%.

Cystoscopy and left retrograde pyelography revealed narrowing of the left ureter and hydronephrosis (Fig. 1). Selective left renal angiography and cavography revealed complete obstruction of the left renal vein (Fig. 2).

Five days later the left kidney and ureter were explored. A retroperitoneal tumour was discovered which was strangulating the ureter and renal pelvis. Left nephroureterectomy with excision of the tumour was performed. The pathological diagnosis was anaplastic carcinoma involving the ureter. Ten days post-operatively jaundice appeared. The patient became anuric with increasing BUN and serum creatinine. He refused further treatment and subsequently died. Autopsy revealed primary anaplastic carcinoma of the pancreatic tail with involvement of the retroperitoneum.

Comment

This case of carcinoma of the pancreas causing ureteric obstruction is noteworthy in that the patient initially presented with left flank pain and non-function of the left kidney only. Only one case of adenocarcinoma of the pancreas was noted in a series of 10,223 consecutive autopsies with ureteric obstruction (MacLean and Fowler, 1956). A case of bilateral ureteric obstruction due to carcinoma of the pancreas was reported by Schmidt in 1971. Wanuck *et al.* (1973) reported a case of pancreatic carcinoma which presented as ureteric obstruction and histologically masqueraded as primary carcinoma of the ureter until autopsy revealed the true cause of the disease: carcinoma of the pancreatic head with diffuse involvement of the retroperitoneum. In our case, exploration revealed an anaplastic carcinoma that blocked the left ureter. The true nature and extent of the disease were realised only after autopsy as being an anaplastic carcinoma of the pancreatic tail.

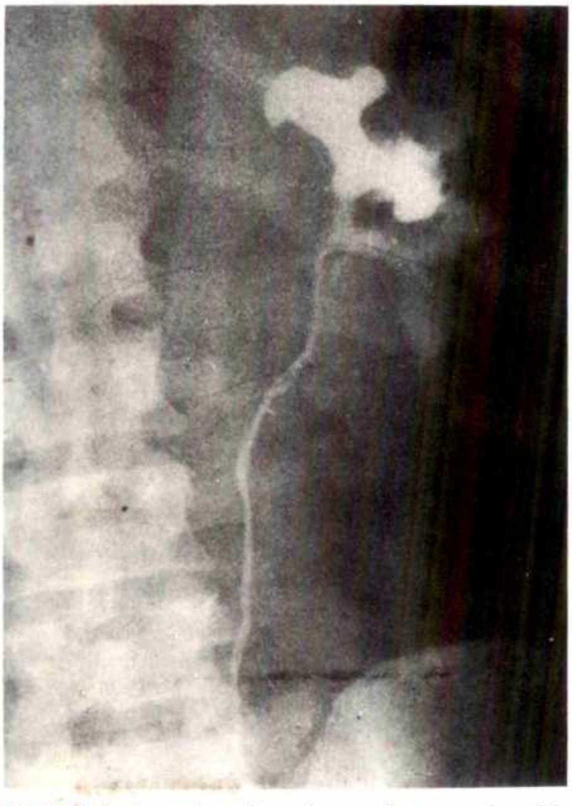

Fig. 1 Left retrograde pyelography revealing narrowing of the left ureter and hydronephrosis.

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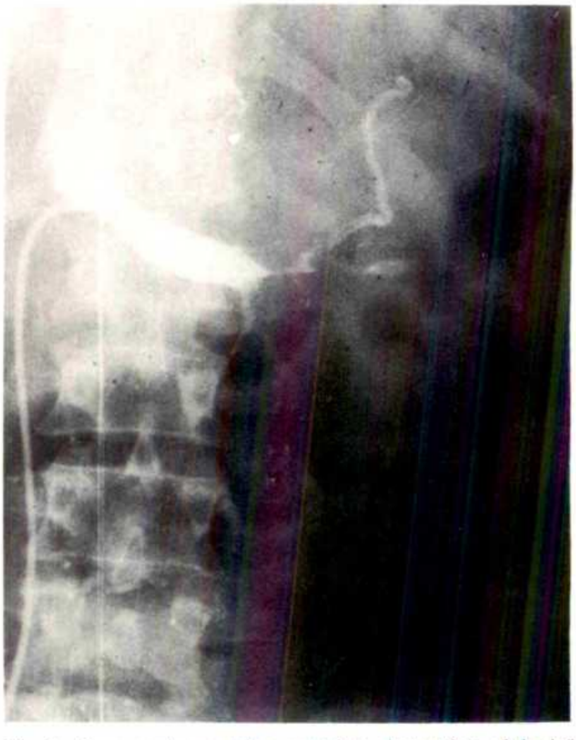

Fig. 2 Cavography revealing complete obstruction of the left renal vein.

Primary Leiomyosarcoma of the Epididymis

R. H. HELM and S. AL-TIKRITI, *Departments of Surgery and Histopathology, Royal Devon and Exeter Hospital, Exeter*

Primary epididymal leiomyosarcomas are rare. There was only one such tumour among 15 paratesticular leiomyosarcomas reported to the UK Testicular Tumour Panel between 1958 and 1967 (Gowing, 1976). A case occurred recently which illustrates several features of this tumour.

Case Report

A 67-year-old man presented with a 2-month history of a swelling in the right side of the scrotum which was not tender and did not fluctuate or transilluminate. There was no lymphadenopathy. A right orchiectomy was carried out, securing the cord at the external ring. On sectioning, an 8 × 6 cm, hard, lobulated, whorled mass was found replacing the epididymis and compressing the intact testis. Microscopy showed a well differentiated leiomyosarcoma with much nuclear pleomorphism but few mitotic figures (Fig.). The cord was free of tumour. The patient made an uneventful recovery and remains well 6 months later.

Comment

Leiomyosarcomas of the paratesticular tissues are rare. They may, theoretically, arise from the walls of epididymal tubules, the cord or their vasculature. The chief characteristics appear to be lack of tenderness, no fluctuation or transillumination; on exploration the mass is found to be hard, lobulated and shows a whorled cut surface. The true incidence of those arising from the epididymis is difficult to determine but two reports have documented three such cases (Davides *et al.*, 1975; Farrell and Donnelly, 1980); the total recorded up to 1980 was 11. Prediction of behaviour is uncertain but it probably does not vary with the exact site of origin. In the experience of the Testicular Tumour Panel (Gowing, 1976), 5 of 15 patients with paratesticular leiomysarcoma died of blood-borne metastases, all within 2 years from the time of orchiectomy, the remaining 10 being alive and well for up to 11 years. Removal of the testis and epididymis after high ligature of the cord is recommended treatment. Pelvic lymph node dissection does not seem justifiable and, as with leiomyosarcomas in general, neither radiotherapy nor chemotherapy is likely to be of further help.

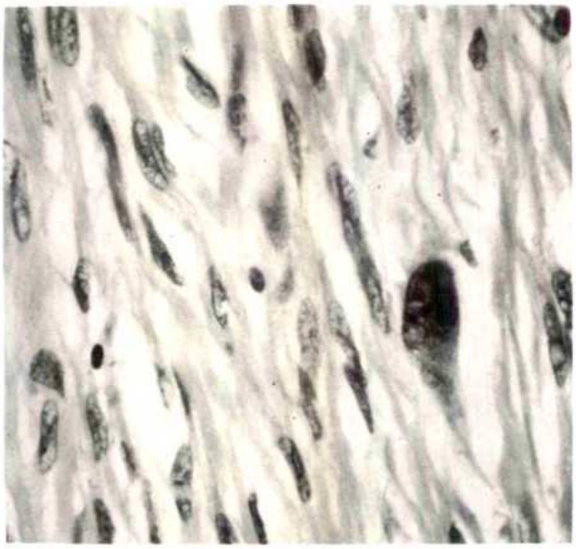

Fig. Elongated spindle cells with oval, blunt-ended nuclei and bizarre, giant, strap-like forms (H and E × 216).

Acknowledgement

We thank Mr T. T. Irvin for permission to report this case and Dr P. P. Anthony for help in preparing the manuscript.

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Requests for reprints to: S. Al-Tikriti, Area Department of Pathology, Church Lane, Heavitree; Exeter, Devon EX2 5DY.

Hibernoma of the Spermatic Cord: the First Reported Case

C. D. M. FLETCHER, *Department of Histopathology*, R. S. COLE, R. L. GOWER and E. HEYDERMAN, *Department of Urology, St Thomas's Hospital, London*

Hibernomas are extremely uncommon benign tumours derived from brown fat: no such lesion has been previously recorded in the spermatic cord.

Case Report

A 10-year-old male presented with a short history of a painful swollen left testis. There was no other relevant history. Torsion was suspected and the scrotum was explored, but at operation there was no evidence of torsion or of any testicular abnormality. However, in the distal spermatic cord there was an ill-defined mass of tan-coloured fatty tissue which was biopsied. Complete excision was not attempted in order to avoid unnecessary damage to vital cord structures.

Histological examination of the biopsy revealed a tumour composed predominantly of large multivacuolated, lipid-laden cells with eosinophilic granular cytoplasm (Fig.) There was also an admixture of univacuolated mature adipose cells. No lipoblasts or mitotic figures were identified.

Comment

Hibernomas are rare tumours derived from brown fat and most often arise in the interscapular region or thigh, usually in adulthood (Enzinger and Weiss, 1983). Their name derives from the fact that brown fat is found predominantly in hibernating animals. In human infants, brown adipose tissue is normally found between the scapulae, in the superior mediastinum and in the retroperitoneum, and is thought to subserve a heat-producing function (Hull, 1966). Such tissue is usually only vestigial and has no known role in adulthood.

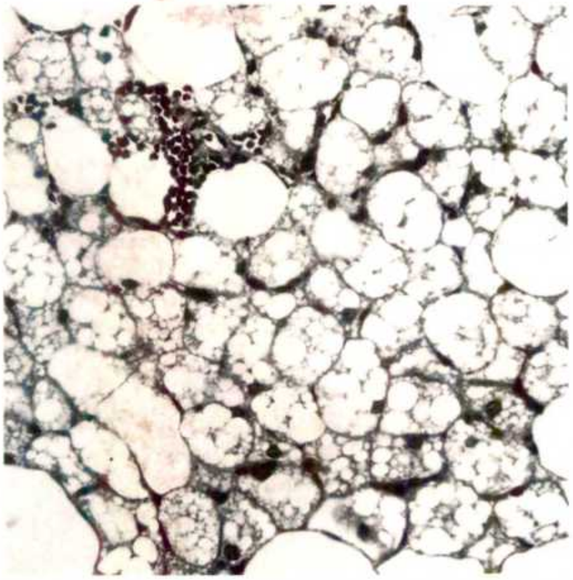

Fig. A medium power view reveals the tumour to be composed of an admixture of univacuolated adipocytes and multivacuolated brown fat cells. There is no nuclear pleomorphism or atypia (H and E × 250).

Hibernomas are slow-growing, painless neoplasms which neither recur, if completely excised, nor have any malignant potential.

This case is most unusual for its location and the age of the patient: it must be assumed that brown fat may migrate, with the testis, from the mesonephric fold adjacent to the kidney.

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Requests for reprints to: C. D. M. Fletcher, Department of Histopathology, St Thomas's Hospital, London SE1 7EH.

Carcinoma of the Prostate in an 11-year-old Child with Long Survival

C. H. CHOW, H. W. LIU, K. W. LEE, H. L. HO and D. SAW,
Surgical and Pathology Units, Queen Elizabeth Hospital, Hong Kong

Malignant tumour of the prostate is a rarity under the age of 21 and most of these tumours are rhabdomyosarcomas and undifferentiated tumours. Shimada *et al*. (1980) reviewed 15 cases of adenocarcinoma (most of them poorly differentiated) from 1912 to 1974 and reported a sixteenth. We report a case of adenocarcinoma in a boy with a longer survival than most reported cases.

Case Report

An 11-year-old Chinese child was admitted in May 1980 with failure to gain weight and recent lower abdominal pain.

Physical examination revealed a marasmic child with body weight and height below the 3rd percentile and head circumference of the 25th percentile. Rectal examination showed a non-tender, uniformly enlarged prostate 4 cm in diameter. Investigations showed a normal blood picture; urea, electrolytes, urine analysis and intravenous urography were also normal. Serum acid phosphatase was 5 iu/l (normal upper limit 5.5). Panendoscopy showed no abnormality. Transrectal needle biopsy showed adenocarcinoma with strong acid phosphatase activity. Total cystectomy, prostatectomy and uretero-sigmoidostomy (Leadbetter type) were performed in June 1980.

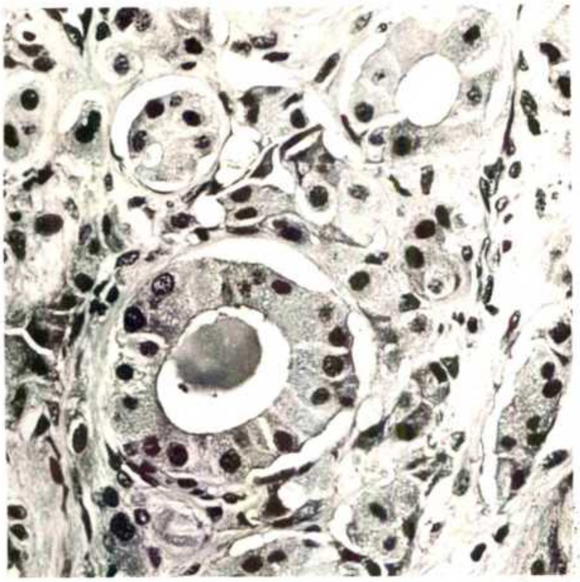

Fig. Moderately differentiated carcinoma with well formed glandular structures as well as ill-defined tubules and clumps of cells infiltrating the fibromuscular stroma. (H and E × 162).

Histological examination confirmed a moderately differentiated carcinoma in a uniformly enlarged prostate infiltrating the seminal vesicle, nerves and bladder muscle (T4 N0 M0). Post-operative bilateral hydronephrosis improved markedly on the right side after 6 months. Stilboestrol 1 mg daily was started 2 years after operation when serial bone scan, performed because of generalised bone pain, showed metastatic lesions in the right mandible and bilateral ribs. Serial acid phosphatase then was 5.5 iu/l. The latest bone scan in January 1984 showed a similar appearance. Acid phosphatase is now 7.7 iu/l.

Comment

This patient is still alive more than 3 years after operation. The following features were different from those of other reported cases:

(1) Long history of symptoms.
(2) Differentiation of tumour cells with strong acid phosphatase reaction.
(3) Long survival.

Reference

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Requests for reprints to: C. H. Chow, c/o Surgical Unit, Queen Elizabeth Hospital, Kowloon, Hong Kong.

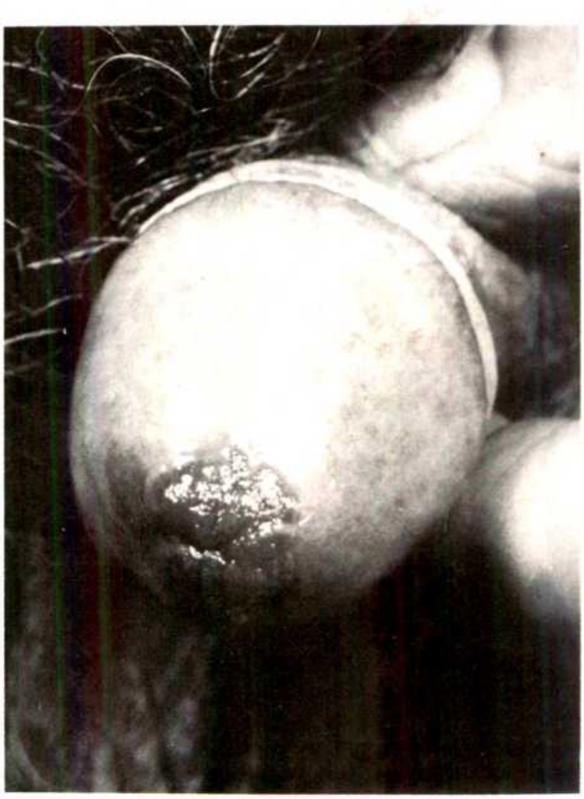
Transitional Cell Carcinoma of the Glans Penis

C. R. JONES and GRANT B. WILLIAMS, *Departments of Urology, Royal Marsden Hospital and Charing Cross Hospital, London*

Epithelial malignancies of the urinary bladder with secondary involvement of the glans penis are rare. We report a case of transitional cell carcinoma presenting as a lesion on the glans penis without a detectable primary in the urothelium

Case Report

A 72-year-old man with a 12-month history of prostatism was referred by his general practitioner. On examination he was noted to have a small, red, cauliflower growth around the external urethral meatus (Fig.). He stated that the lesion had been present for several weeks and had appeared after he had accidentally touched the tip of his penis with a block of solid toilet disinfectant. A mid-stream specimen of urine contained some white blood cells with less than 10,000 organisms per ml. An



intravenous urogram was normal. He was admitted for transurethral resection of the prostate and biopsy of the penile lesion. Histological examination of the prostate revealed prostatic hyperplasia with one fragment containing a focus of well differentiated adenocarcinoma (Gleason Grade 1 + 1). The penile biopsy consisted of moderately differentiated papillary transitional cell carcinoma with superficial invasion. Random biopsies showed mild chronic inflammation only.

He made an uneventful post-operative recovery and was referred for radiotherapy.

Comment

In 1961 Abeshouse and Abeshouse presented a comprehensive review of all malignancies metastatic to the penis. They were all secondary tumours and occurred in the late stages of the primary disease as a solitary metastasis or part of a widespread dissemination. Direct infiltration, external dissemination, retrograde venous or lymphatic spread have been suggested as the source of the cells (Deeley and Morrison, 1960). In this case the most probable source was an occult primary lesion of the urothelium.

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Requests for reprints to: C. R. Jones, Department of Urology, St Mary's Hospital, Praed Street, London W2 1NY.

Vesicorectostomy

E. KOSKELA, *Department of Surgery, Oulu University Central Hospital, Oulu, Finland*

Deviation of the urinary flow by vesicorectostomy is little known and was first reported by Moore (1954). In our case vesicorectostomy was used to solve the problems of severe urethral stricture and incontinence.

Case Report

A 73-year-old man underwent prostatectomy in May 1970 for prostatic hyperplasia with unstable bladder activity. Because his urinary disorders continued the prostatic residue was resected 2 years later. However, urinary incontinence became so severe that Kaufman-type incontinence prostheses were inserted on six occasions between 1973 and 1976. Eventually the prosthesis disrupted the urethra, which became completely obstructed. A suprapubic cystostomy was made but infection, urinary leakage and pain made it so unpleasant that in January 1977 a vesicorectostomy was performed by constructing a 2-cm transverse oval stoma between bladder and rectum just proximal to the trigone. The patient remained continent post-operatively and took methenamine hippurate 0.5 g twice daily prophylactically.

He remained well for over 2 years. Intravenous urograms were normal. Serum urea, urate, creatinine, ASAT and ALAT were all normal and he did not have pyelonephritis. He voided every 2 to 5 h by emptying the bladder into the rectum (Fig.) and then emptying the rectum. Voiding urine and emptying the bowel occurred separately.

Over 2 years after this operation the patient died from pneumonia following an operation for fracture of the femoral neck.

Comment

Vesicorectostomy may be useful for obstructive lesions distal to the vesical neck and for incontinence which fails to respond to the usual methods of treatment. Rectal continence is a prerequisite for this simple operation, which can be reversed (Kil-

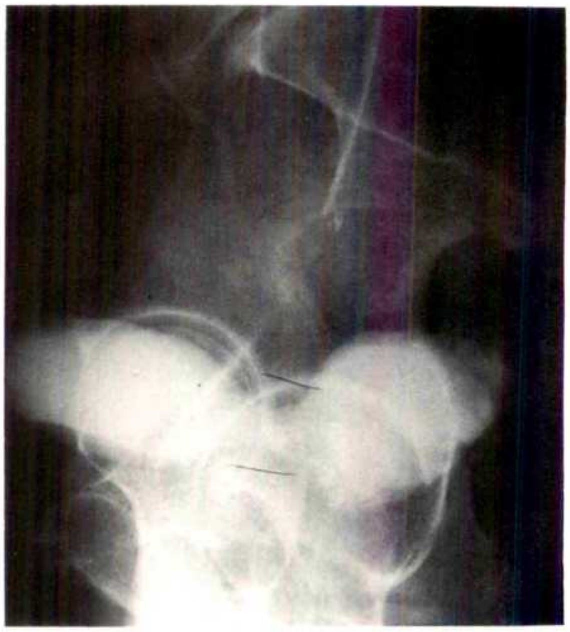

Fig. Emptying of the bladder into the rectum through the vesicorectostomy after intravenous urography.

patrick and York Mason, 1969). The most frequent complication is stenosis of the anastomosis. There is no need for tubes, catheters or other appliances. The longest follow-up times are 17, 18 and 22 years (Rabinowitz *et al.*, 1976).

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Requests for reprints to: E. A. Koskela, Rusthollarintie 3E, SF-00910 Helsinki 91, Finland.

Tuberculous Stricture of Ureter. A New Method of Intubated Ureterotomy

D. E. OSBORN, N. J. RAO and N. J. BLACKLOCK, *Department of Urology, University Hospital of South Manchester, Manchester*

The surgical treatment of genito-urinary tuberculosis has become progressively conservative with the development of effective chemotherapy. A case is reported in which multiple ureteric strictures did not respond to anti-tuberculous treatment and required ureteric splinting, after which serial gamma camera renograms demonstrated that renal function was preserved.

Case Report

A 55-year-old patient with upper, middle and lower ureteric strictures in one kidney from tuberculosis developed progressive obstruction after 4 months of chemotherapy. Renograms demonstrated that the function of this kidney had fallen from 44 to 17% of overall function. The ureter was therefore explored. It was grossly thickened and up to 2 cm in diameter (Fig.) After making ureterotomies at the stricture sites a silastic tube (Dow Corning 0.192 inch external diameter) was inserted from the renal pelvis to the bladder and an omental wrap placed around the ureter. Nine months later the splint was removed endoscopically. After ureteric splinting the function of this kidney improved to 33% of overall function and remains at this level 15 months later.

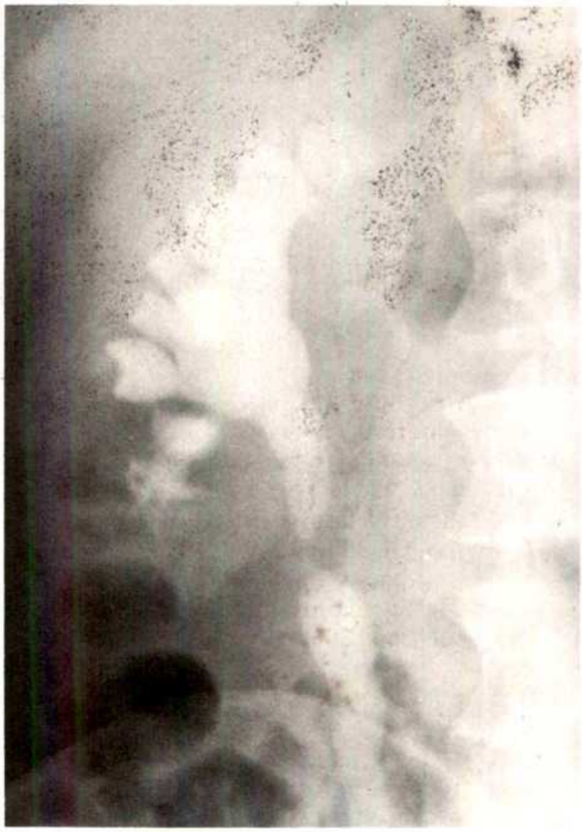

Fig. The upper ureteric stricture immediately before exploration.

Comment

Tuberculous stricture of the lower ureter that persists and cannot be dilated endoscopically may need ureteric reimplantation with, when necessary, a psoas hitch procedure or Boari flap. Stricture of the middle and upper third of the ureter is uncommon and less easy to treat. Davies *et al.* (1948) demonstrated both experimentally and clinically that upper ureteric strictures could be successfully treated by making a ureterotomy at the stricture site and leaving an indwelling ureteric splint. The usefulness of this technique for tuberculous ureteric strictures has been subsequently confirmed by Moore *et al.* (1969). The advantage of using a silastic tube splint is that it avoids a nephrostomy or ureterostomy and allows normal voiding of urine. Silastic ureteric splints can therefore be left for many months and we have used them for up to a year following ureterolysis for retroperitoneal fibrosis (Osborn *et al.*, 1981).

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Requests for reprints to: D. E. Osborn, Department of Urology, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW.

Non-specific Segmental Ureteritis

D. KIMCHE and D. LASK, *Department of Urology, Hasharon Hospital, Petah Tiqva, and Sackler School of Medicine, Tel-Aviv University, Israel*

Non-specific segmental ureteritis is a rare entity of uncertain aetiology often presenting with lower back pain, haematuria and a unilateral, tumour-like ureteric obstruction.

Case Report

A 42-year-old male presented with a 5-month history of spastic pain in the right lumbar region and macroscopic haematuria. Six years previously he had secreted a small stone without haematuria. Physical and laboratory examinations were unremarkable. Urine examination for mycobacteria, fungi and helminths was negative. Intravenous urography showed a marked narrowing of the right ureteric lumen at the level of S2, with consequent dilatation of the right pelvis and the ureter above this area but no ureterolithiasis (Fig. 1). On exploration, a 3-cm-long area of induration was detected in the ureteric wall. The distal part of the ureter was normal. Since frozen section was negative for malignancy, a segmental resection and end-to-end anastomosis of the ureter were performed. The excised portion of the ureter revealed almost complete destruction of the mucous membrane owing to haemorrhage in the submucosa and a non-specific inflammatory infiltrate in the ureteric wall (Fig. 2).

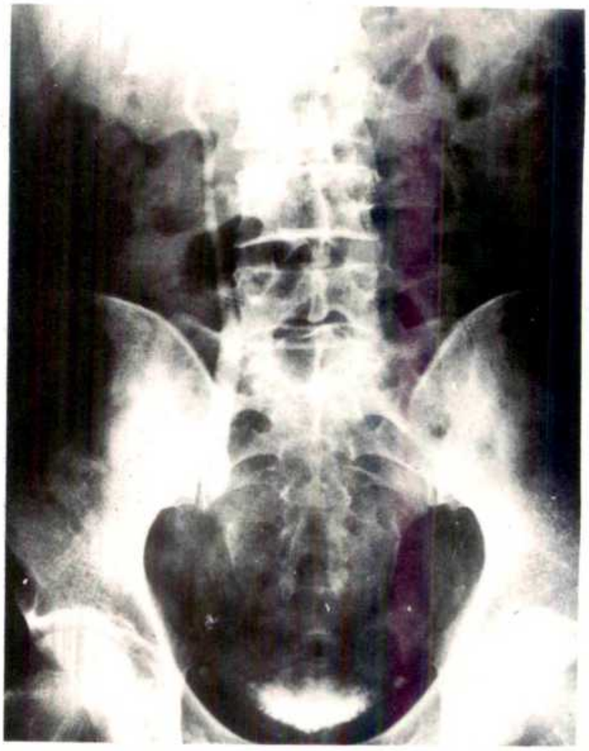

Fig. 1 Pre-operative intravenous urography.

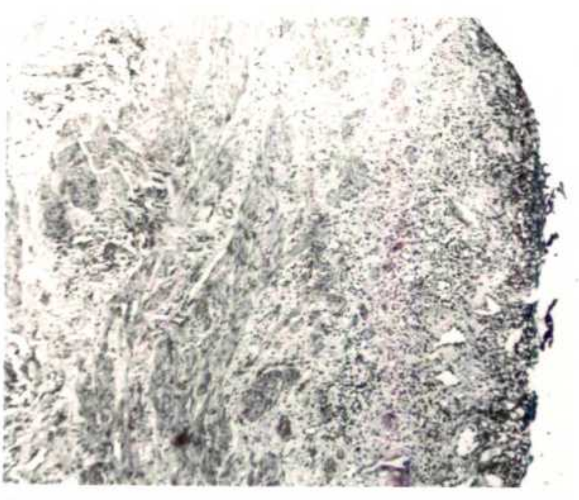

Fig. 2 Excised ureteric segment showing massive haemorrhage and non-specific inflammatory infiltration. (H and E × 25).

Comment

Cases of non-specific ureteritis usually present with spastic lower back pain, urinary tract infection and haematuria. The microscopic picture is protean and may include non-specific granulomatous reaction around crystalline material or a small stone within the ureteric wall, cellular infiltration, proliferation of capillaries, fibrocytes and giant cells and, in some instances, numerous abscesses in the submucosal layer (O'Flynn, 1963; Storm and Fallon, 1977).

The striking features in our case were the prolonged gross haematuria and the absence of a stone in the urinary tract on admission. Considering, however, our patient's earlier history of urolithiasis and the report by Schwartz (1972) of ureteritis in a patient following stone expulsion, it is possible that a stone passed during a previous episode of renal colic may have caused the changes in the ureter. Another possibility could be a vascular, occlusive process leading initially to infarction of the ureteric segment and subsequently to a non-specific inflammatory reaction.

References

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Schwartz, D. T. (1972). Transient nonspecific regional ureteritis following passage of ureteral stone. *Journal of Urology*, **107**, 740-742.

Storm, P. B. and Fallon, B. (1977). Non-specific granulomatous ureteritis. *Journal of Urology*, **117**, 794-795.

Requests for reprints to: D. Kimche, Department of Urology, Hasharon Hospital, Petah Tiqva, Israel.

Adenoid Cystic Carcinoma of the Prostate

A. M. GILMOUR and T. J. BELL, *Department of Histopathology, St Thomas' Hospital, London, and Urology Department, District General Hospital, Eastbourne*

Adenoid cystic carcinoma is a rare variant of prostatic carcinoma. A case is described and the literature reviewed.

Case Report

A 76-year-old man presented with a 5-year history of urinary frequency, nocturia and poor stream. There was no dysuria or haematuria. A transurethral resection was carried out and 31 g of prostate removed. Post-operative recovery was uneventful and he remains well 8 months later.

Histological examination of the resected tissue showed fibro myo-adenomatous hyperplasia in some fragments but elsewhere there was widespread infiltrating carcinoma showing the classical adenoid cystic pattern (Figs 1 and 2).

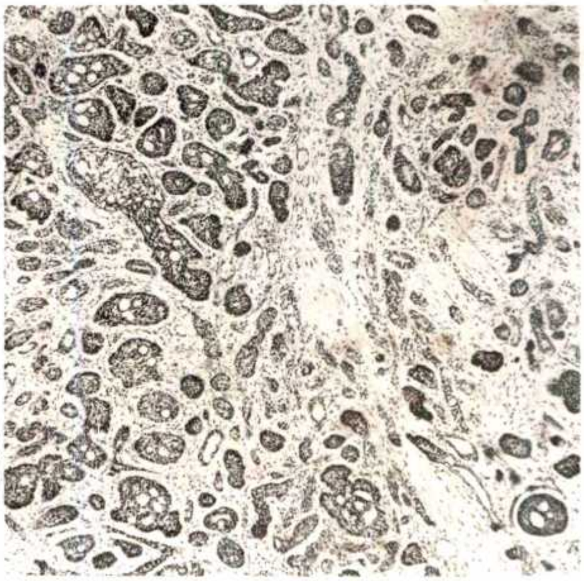

Fig. 1 Irregular nests, cords and tubules composed of basaloid cells set in a fibromuscular stroma. (H and E × 63).

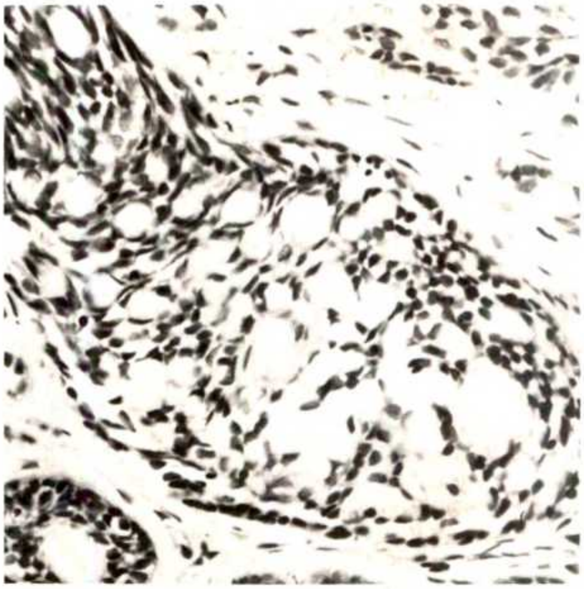

Fig. 2 Large cell nest shows the typical cribriform (sieve-like) pattern. (H and E × 100).

Comment

Adenoid cystic carcinoma is a histologically distinctive neoplasm which occurs most often in the major and minor salivary glands. It is usually of low grade malignancy but may show local and peri-neural infiltration and later lymph node metastases. These tumours have also occurred in the upper respiratory tract, breast, oesophagus and cervix.

Four cases of this neoplasm occurring as a primary tumour in the prostate have been reported (Frankel and Craig, 1974; Tannenbaum, 1975; Kramer *et al.*, 1978). In three cases the tumour had spread outside the prostatic capsule at presentation. The fourth patient was free of recurrence 3 years later. Survival times were not reported, however, and little is known of the clinical behaviour of these tumours or their response to anti-androgen therapy.

References

Frankel, K. and Craig, J. R. (1974). Adenoid cystic carcinoma of the prostate—report of a case. *American Journal of Clinical Pathology*, **62**, 639-644.

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Tannenbaum, M. (1975). Adenoid cystic or "salivary gland" carcinoma of prostate. *Urology*, **VI**, 238-239.

Requests for reprints to: A. M. Gilmour, Department of Histopathology, District General Hospital, Kings Drive, Eastbourne, Sussex BN21 2UD.

Adrenal Cyst

F. S. BARBOSA, *Department of Urology, Broadgreen Hospital, Liverpool*

Case Report

A 57-year-old female was admitted with pain in the left hypochondrium. On examination a large cystic mass, moving on respiration, was palpable in the left hypochondrium.

A plain abdominal X-ray revealed an 11 cm round calcified shadow above the left kidney (Fig. 1). An IVU showed what seemed to be a large cyst in the upper pole of the left kidney (Fig. 2). Ultrasound suggested a cystic mass in a duplex kidney. On exploration a large cystic mass was found, completely detached from the left kidney but rising from the adrenal gland. The cyst was removed and histological examination showed a thick walled cyst of 11 cm containing white material, partly calcified and showing fibrin surrounded by cortical adrenal tissue.

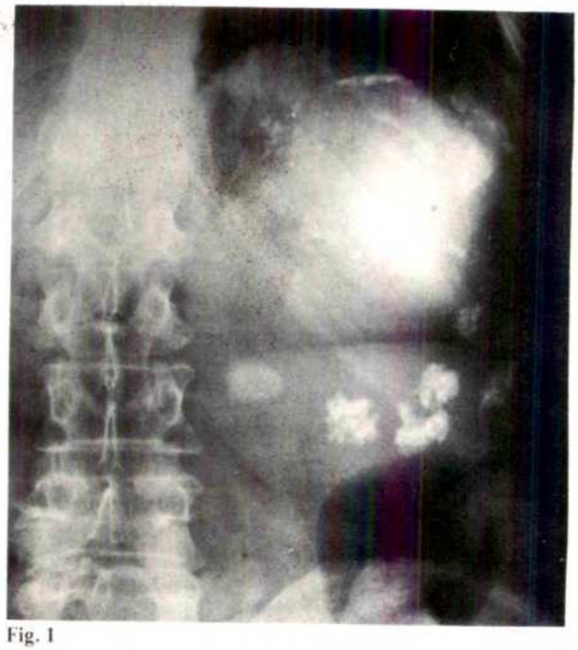

Fig. 1

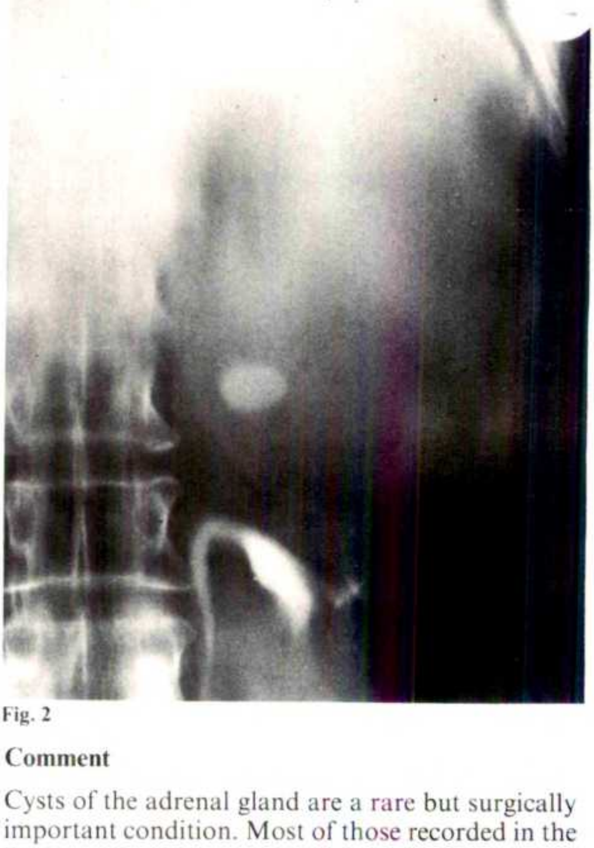

Fig. 2

Comment

Cysts of the adrenal gland are a rare but surgically important condition. Most of those recorded in the literature have been small lesions found accidentally at autopsy. Until 1966 approximately 220 adrenal cysts had been reported (Foster, 1966) and Uretzky *et al.* (1978) reported a further three cases.

Symptomatic and palpable adrenal cysts should be removed in order to alleviate symptoms and to prevent complications such as haemorrhage, infection and hypertension.

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Foster, D. G. (1966). Adrenal cysts: review of literature and report of case. *Archives of Surgery*, **92**, 131-143.

Uretzky, G., Freund, H., Charuzi, I. and Luttwak, E. M. (1978). Cysts of the adrenal gland. *European Urology*, **4**, 97-99.

Requests for reprints to: F. S. Barbosa, Department of Urology, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB.

Eosinophilic Nephro-ureteritis

J. A. MASSEY, *Department of Urology, Royal Infirmary, Preston*

Case Report

Eosinophilic pyelo-ureteritis has been described on one occasion by Hellstrom *et al.* (1979). A case of eosinophilic nephro-ureteritis with similar histological features is now reported and a possible cause for the condition suggested.

A 68-year-old male presented with haematuria and left-sided clot colic after 2 years' discomfort in the left loin. There were no other urinary symptoms. On examination there was no tenderness; he had a 60 g benign prostate and the scar of an extensive "palliative" gastrectomy, cholecystectomy and liver biopsy carried out 4 years previously for macroscopically invasive linitis plastica. Histological examination had shown only eosinophilic infiltration in all three organs.

The ESR was 62 mm/h and the urine was sterile. IVU and cystoscopy initially revealed no causative lesion. The symptoms regressed and then recurred, and another IVU 3 months later showed distortion of the central calices on the left (Fig.). Nephro-ureterectomy was performed for a central renal mass with extensive infiltration of the pelvis and ureter. Histological examination showed fibrosis and eosinophilic infiltration identical to that noted earlier in the gastric specimen.

We noted a progressive infiltration in chest X-rays over the 4 years since gastrectomy had been performed (they had previously been clear). Cultures of sputum but not urine had proved positive for tuberculosis. The patient remains well on treatment.

Comment

Eosinophilic gastro-enteritis has been found predominantly in middle-aged males with a history of allergy and asthma (Ming, 1973) and no association has been described with eosinophilic cystitis or pyelo-ureteritis despite similar histological appearances (Hellstrom *et al.*, 1979). However, Manko *et al.* (1972) reported asymptomatic post mortem evidence of minimal renal involvement in a case of disseminated hypereosinophilic disease.

There was no history of allergy or asthma in this patient but we suggest the possibility of an allergic reaction to the tubercle bacillus as occurs in the retest phenomenon.

Acknowledgements

I thank Mr R. G. N. Thomson and Mr J. Russell for permission to report on their patient and I am grateful to Dr W. G. Owen, Consultant Pathologist, for advice on the histology.

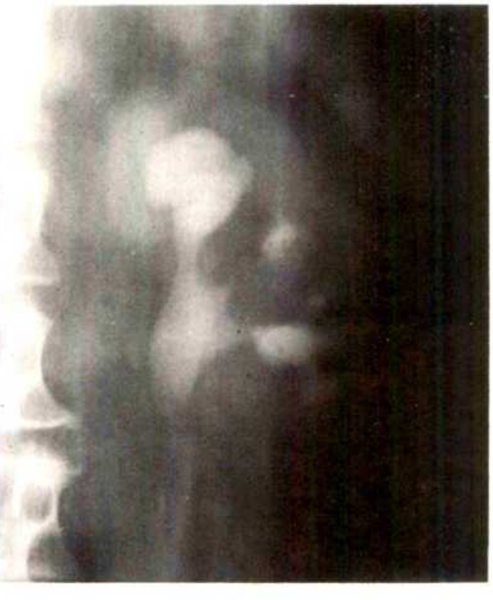
References

Hellstrom, H. R., Davis, B. K., Shonnard, J. W. and MacPherson, T. A. (1979). Eosinophilic pyelo-ureteritis: report of a case. *Journal of Urology*, **122**, 833-834.

Manko, M. A., Cooper, J. H. and Myers, R. N. (1972). Disseminated hypereosinophilic disease. *American Journal of Gastroenterology*, **57**, 318-325.

Ming, Si-Chun (1973). In *Tumors of the Esophagus and Stomach*. P. 104. Washington: Armed Forces Institute of Pathology.

Requests for reprints to: J. A. Massey, The Investigative Unit, Department of Urology, Ham Green Hospital, Pill, Bristol.



British Journal of Urology (1986), **58**, 108-109

Notices

British Association of Urological Surgeons and Canadian Urological Association

Presidents: Professor J. P. Blandy, MA, DM, MCh, FRCS, FACS
Dr G. A. Farrow, MD, FRCS(C), FACS

Annual Meeting: London, 17–20 June 1986

All correspondence to: R. G. Notley, MS, FRCS, Honorary Secretary, British Association of Urological Surgeons at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

DANTEC Urology Prize

An annual prize (formerly known as the DISA Urology Prize) will be awarded by DANTEC for the best scientific paper contributing towards the understanding of urinary tract function which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will consist of a travel voucher for £400.00 and a token presentation gift. The winner will be notified before the BAUS Annual Meeting and the prize will be presented at the meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered.

All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to: The Honorary Secretary, The British Association of Urological Surgeons at The Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN.

Shackman Travelling Fellowships 1986

Fellowships have been awarded to Mr D. E. Neal, Newcastle, to study the surgery and function of urinary reservoirs at the Department of Urology, University of Mainz, and to Mr D. F. M. Thomas, Leeds, to enable him to study recent advances in paediatric urology in the United States.

Urological Society of Australasia, 39th Annual Scientific Meeting

Perth, Western Australia, 6-11 April 1986

Further particulars from: A. I. Low, 167 St George's Terrace, Perth 6000, Western Australia.

American Cancer Society: National Conference on Urologic Cancer

Philadelphia, USA, 9-11 April 1986

Further information from: American Cancer Society, National Conference on Urologic Cancer—1986, 90 Park Avenue, New York, NY 10016, USA.

Urological Days of Necker 1986

Paris, France, 13-15 March 1986

The topics will be:

(1) New and unusual forms of treatment for female urinary incontinence.
(2) Percutaneous extraction of upper urinary tract stones.
(3) Intestinal grafts in paediatric urology.

Further information from: Professor J. Cukier, Clinique Urologique, Hôpital Necker, 149 Rue de Sèvres, 75743 Paris Cédex 15, France.

Fifth Basic Urodynamics Course

Bristol, 12 April 1986

The topics will include:

Anatomy and physiology
Basic techniques
Urodynamic equipment
Clinical applications in urology, gynaecology and spinal injuries

Further particulars from: P. Abrams, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

Athenian Days of Urology 1986

Athens, Greece, 9-11 May 1986

The topics will be:

(1) What's new in urology?
(2) Extracorporeal lithotripsy.

Further information from: Professor C. Dimopoulos, Laikon Hospital, 11527 Athens, Greece.

Second World Meeting on Impotence and Fifth Conference on Vasculogenic Impotence and Corpus Cavernosum Revascularisation

Prague, Czechoslovakia, 17-20 June 1986

Topics will include research on the physiology and haemodynamics of erection, morphological (angiographic) and functional examination of cavernous bodies of afferent and efferent vascular and neural pathways, and conservative and surgical treatment.

A pre-Congress teaching session will be held on 16 June 1986.

Further information from: V. Michal, Institute for Clinical and Experimental Medicine, Videnska 800, 146 22 Prague 4, Czechoslovakia.

Fourth International Forum of Andrology

Paris, France, 19-20 June 1986

The following topics will be discussed:

Prostatitis, acute and chronic
Male contraception
Male sterility: hormonal causes
What's new in andrology (posters)

Further particulars from: Professor G. Arvis, Department of Andrology-Urology, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, F-75012 Paris, France.

Workshop on Testicular Tumours

Copenhagen, Denmark, 16-19 August 1986

The programme will include lectures and free communications on the following topics: morphology and function of the germ cell, cell lines, chromosome markers and oncogenes, histochemistry and monoclonal antibodies, carcinoma *in situ*, screening, prognostic factors, treatment, toxicity, and fertility.

Further information from: Dr M. Rørth, Department of Oncology II, Finsen Institute, 49 Strandboulevarden, DK-2100 Copenhagen, Denmark.

Fifth Congress of European Society for Urological Oncology and Endocrinology

Edinburgh, 18 and 19 August 1986

The programme will include plenary lectures by invited speakers, free communications and poster sessions on the following topics: oncogenes and growth factors, prostate receptors and metabolism, stromal/epithelial interactions, urological tumour markers, and hormone independent tumours and tumour resistance.

Further particulars from: F. K. Habib, Department of Surgery/Urology, University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG.

International Society for Dynamics of the Upper Urinary Tract

Newport, USA, 14-16 September 1986

Further information from: Dr B. L. R. A. Coolsaet, Noordheuvel 50, 2170 Wuustwezel, Belgium.

British Journal of Urology (1985), 58, 110-112
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Book Reviews

The Kidney: Physiology and Pathophysiology. Volumes 1 and 2. Edited by D. W. Seldin and G. Giebisch. Pp. 2162. New York: Raven Press. 1985. Price for both volumes: US$289.50.

These two volumes must represent the most complete treatise on the physiology and pathophysiology of the kidney. Those who recall Homer Smith's 220-page little book on the Principles of Renal Physiology (1956) will appreciate the phenomenal increase in the subject matter in 30 years. In those earlier days the emphasis was on methods of measuring glomerular filtration rate, renal blood flow and tubular function in the normal and abnormal kidney. Since then the role of the kidney as a regulator of so many body functions has gradually been defined and clarified.

There are four main sections: i. General principles of electrolyte regulation; ii. Organisation of the kidney; iii. Water and electrolyte exchanges; iv. Extrinsic and intrinsic renal failure. The two volumes are encyclopaedic and the 2100 pages are full of data and often very daunting. However, this is a first class reference text and for the urologist interested in the various aspects of renal failure Section iv must be the best reference source: this section includes chapters on the pathophysiology of various subjects ranging from the hepato-renal syndrome, urinary tract obstruction, pregnancy-related disease as well as acute and chronic renal failure.

Clinical Dialysis. Edited by A. R. Nissenson, R. N. Fine and D. E. Gentile. Pp. xiii + 737. Norwalk, Connecticut: Appleton-Century-Crofts. 1984. Price £87.55; US $114.75.

Over the past decade there has been a dramatic increase in the number of patients with end stage chronic renal failure, maintained by dialysis therapy. Over the same period there has been an equally dramatic increase in our understanding of the basic principles of dialysis and of complications associated with treatment. These advances have resulted in better application of dialysis therapy to the patient, thus contributing to improved survival and quality of life. In addition, it should now be possible to prevent many major complications. Until recently no textbook was available which provided an up-to-date, detailed account of the basic principles of dialysis and its complications, and which also dealt with the clinical application of dialysis therapy. It was, therefore, difficult for a doctor training in nephrology to become conversant with all aspects of dialysis.

This book fills a major gap by providing a comprehensive account of dialysis, covering both basic principles and clinical application. It is a multi-author book which is in general well written, many of the authors being recognised authorities in their field. It is up-to-date and well referenced. Although the accounts of the basic principles of dialysis and its complications are excellent, those on clinical management are at times somewhat impractical. Nevertheless, this book will be of immense value to doctors training in nephrology or as a reference source for practising nephrologists. While at £87.55 it appears very expensive, it is strongly recommended as an essential addition to the library of any department where haemodialysis or peritoneal dialysis is a regular therapy.

Current Operative Urology. Edited by E. D. Whitehead and E. Leiter. Second edition. Pp. xliii + 1692. London: Harper & Row. 1984. Price £185.25.

There are 235 contributors to this substantial book, which covers virtually every aspect of urological surgery. The format of the first edition has been retained and consists of commentaries based on a publication on a particular topic. Each topic has then been reviewed by an overviewer.

This format has both advantages and disadvantages. Certainly this is not the ideal format for quick and ready reference to details of a particular operation, but it does allow more room for thought-provoking and controversial ideas on the philosophy of the surgical approach.

The book is full of interest and is well produced. At £185 it may not find a place on every individual surgeon's bookshelf but it is recommended for urological departmental libraries.

Clinical Pediatric Urology. Edited by P. P. Kelalis, L. R. King and A. B. Belman. Second edition, volumes I and II. Pp. 1286. Eastbourne: Baillière Tindall/Saunders. 1985. Price £69 each volume.

The appearance of the second edition of Clinical Pediatric Urology after 8 years is a timely addition to the literature in this speciality, where significant advances have been made during that time. It provides a comprehensive review of the subject by 56 authors, most of whom practise in the United States. Despite this multiplicity of authors the volumes have been well edited, so that each chapter retains the author's original style. The chapters on diagnostic imaging have been extensively revised and reflect modern-day practice. Urinary incontinence, vesicoureteric reflux, obstructive uropathy and hypospadias provide the basis for comprehensive reviews. In a speciality where individual surgeons will see rarities infrequently, this book provides advice based on extensive clinical experience backed with many up-to-date references. The illustrations are excellent, tables, diagrams and X-rays all being well reproduced. The price may deter most individuals from purchasing these volumes, but they are an essential addition to the library of any centre where children's urological surgery is practised.

Précis d'Urologie de l'Enfant. By P. Mollard. Pp. xii + 387. Paris: Masson. 1984. Price Fr F 495.

This book, entirely in French, covers the entire field of paediatric urology in a logical and comprehensive way. This reviewer may have missed a few of the finer points, but the discussions of recent advances seem up-to-date.

There are full references at the end of each chapter and most recent papers are included. Reproduction of X-rays is excellent but the line drawings are generally of very poor quality and the clinical photographs are often out of focus. Some of the chapters, rightly, reflect the author's personal choice of operation but in the section on hypospadias, for instance, the description of the splendid MAGPI operation would be insufficient for the novice to learn this technique. He would need to turn to a more detailed description elsewhere.

This book will make interesting reading for urologists in French-speaking countries, for whom it is clearly intended.

Clinical Paediatric Uroradiology. By I. A. Aaronson and B. J. Cremin. Pp. 456. Edinburgh: Churchill Livingstone. 1984. Price £75.00.

The depth of information in this splendid book is a testament to the enormous experience of a paediatric urologist and a radiologist working in Cape Town. Each chapter taken in isolation is a masterpiece and together they make a tome which is a major contribution to paediatric urology and radiology. There are no glaring omissions amongst the chapters and each is illustrated with a profusion of clinical photographs and X-rays of excellent quality, chosen, the authors say, from many thousands that were taken in the preparation of the book. Attractive features are the flow charts and lists that abound in the text, making the management of such conditions as haematuria or intersex seem like child's play. References at the end of each chapter are up-to-date and topic-related.

Modern investigative techniques of scintigraphy, ultrasound, CT and NMR are all included and the book would not have been complete without the famous Cremin view of the dilated posterior urethra in boys with a urethral valve as seen by ultrasound via the perineum.

Typographical errors are few and it is probably only a coincidence that two colleagues of the reviewer have their names spelt incorrectly. Ureterocele is consistently mis-spelt as ureterocoele.

The book will be a prized possession for all those wise enough to invest in this particular commodity, i.e. the vast experience of another clinician arduously transcribed for painless reading.

Tumors of the Kidney and Urinary Tract. Colour Atlas and Textbook. By S. Olsen. Pp. 291. Copenhagen: Munksgaard. 1984.

As its title implies, this book is more than just a colour atlas of tumours of kidney and urinary tract. The text which accompanies the illustrations is succinct, clear and remarkably comprehensive. References are given to the more important papers and these are helpful and well chosen. The illustrations of gross and microscopic preparations are outstanding: these are supplemented by a selection of electronmicrographs.

The author follows the WHO classification of tumour typing, and those of kidney and urinary bladder are given in the appendices. However, one would like to have seen something of more newly recognised renal tumours of infancy, *e.g.* clear cell sarcoma of kidney and rhabdoid tumours of kidney. A discussion of the points of distinction between these and more familiar infantile renal neoplasms—nephroblastoma and mesoblastic nephroma—would also have been timely and helpful. Admittedly the author places considerable emphasis in the text on differential diagnosis of the tumours discussed but on the whole the reviewer did not find this particularly helpful. However, these are minor criticisms of what is an excellent production which will be of value both to urological surgeons and to pathologists who require a concise, well illustrated account of these tumours.

Urinary Tract Trauma. By J. P. Mitchell. Pp. xviii + 276. Bristol: Wright. 1984. Price £29.50.

Professor Mitchell is an acknowledged authority on injuries of the urinary tract and has written many articles and chapters on the subject. This book assembles in one volume his views on the assessment and treatment of urinary tract injuries derived from the 30 or more years' experience he has had since founding the Bristol Trauma Project, a project that has enabled him to study prospectively patients with urinary tract injuries referred to the Department of Urology in Bristol.

However, the book does more than present his own and his colleagues' views on the subject and on the plan of management they have developed in Bristol; it also discusses the merits of other forms of treatment, provided they are supported by a reasonable amount of experience. Professor Mitchell rightly assumes that readers of this book will be familiar with the general effects of injury such as shock, and with the need to exclude associated injuries which may not at first be obvious, and he does not discuss the effects upon renal function of prolonged hypotension, extensive muscle and tissue destruction and infection; otherwise the book is comprehensive. It is well illustrated and very readable, with many anecdotal and highly instructive accounts of patients scattered throughout the text. This book should be readily available to all those who are involved in the management of abdominal or pelvic trauma.

1984 Year Book of Urology. Edited by J. Y. Gillenwater and S. S. Howards. Pp. 308. Chicago: Year Book Medical Publishers. 1984. Price £45.00.

The Year Book remains an interesting tour de force by its editors. The selection of 254 articles from 3500, summarising them and offering a useful comment, represents an enormous task. As with previous volumes in this series, it remains an interesting book, but with the massive number of journals, reviews and meetings it must be doubted whether any but a few urologists can do justice to the quality of work put into the preparation of this volume. The introductory six pages are particularly useful as a perspective on the many current changes in urology. This book is well worth reading, especially for the review of subjects that are peripheral to the main interests of the reader.

Cancer of the Kidney. Edited by N. Javadpour. Pp. viii + 172. Stuttgart, New York: Thieme Verlag. 1984. Price DM 128,-.

The reader of a book on renal carcinoma will know that this tumour is and remains very frustrating to treat. The variable natural history can give a false security but when the disease does progress, what are the possible treatments? This book has no new answers but gives a good summary of present opinion. The section on immunotherapy reaches a fair conclusion, *i.e.* that it is difficult to assess the immunotherapeutic response in renal cancer, but in this and other treatment sections there is a general lack of critical comment on reported experience. For a book devoted to one malignancy, many topics such as angio-infarction, oncocytoma or the value of radical surgery are too sketchy for the specialist and this book will be of most value to either non-urologists or urologists in training.

Nephrology. Proceedings of the IXth International Congress of Nephrology. Volumes I and II. Edited by R. R. Robinson. Pp. 1756 (Volume I: 1-884; Volume II: 885-1756). Berlin, Heidelberg, New York, Tokyo: Springer-Verlag. 1984. Price DM 380,--.

These two volumes are the Proceedings of the International Nephrology Conference in Los Angeles in 1984. They represent an extremely comprehensive coverage of the subject and it is immediately evident that these are no ordinary proceedings volumes. The papers are well prepared contributions to work-shops, symposia and state of the art lectures. This format and diversity of material make these two volumes the most up to date text on the subject. Urologists will find a number of sections of relevance, including obstructive uropathy, urolithiasis, infection, reflux nephropathy, the kidney and malignant disease, as well as many aspects of dialysis and transplantation. These volumes are a striking example of the exception to the rule that most proceedings are poorly presented and lack editorial control. They will easily remain an important reference source until the next conference, in London, in 1987.

Books Received

La Biopsie Testiculaire. Edited by G. Arvis and J. P. Dadoune. Pp. 104. Paris: Masson. 1985.

Advances in Nephrology. Volume 14. Edited by J. P. Grünfeld and M. H. Maxwell. Pp. xxvi + 518. Chicago: Year Book Medical Publishers. 1985. Price £59.50.

Manual of Renal Disease. By C. B. Brown. Pp. 227. Edinburgh: Churchill Livingstone. 1985. Price £7.95.

Medical Terminology. A Guide to Current Usage. By P. M. Davies. Pp. 365. London: Heinemann. 1985. Price £10.00.

Cephradine 12 Years on. A Routine Antibiotic for Therapy and Prophylaxis. Edited by A. Percival and L. Woods. Pp. xi + 121. Oxford University Press for the Royal Society of Medicine. 1985. Price £12.00.

Diuretics in Heart Failure. Edited by L. E. Ramsay. Pp. viii + 92. Oxford University Press for the Royal Society of Medicine. 1985. Price £9.00.

Proteinuria. Edited by M. M. Avram. Pp. xvi + 232. New York, London: Plenum Publishing Corporation. 1985. Price US $35.00.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

ADRENAL

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Adrenal adenomas and adrenal carcinomas in association with hereditary adenomatosis of the colon and rectum. (T. A. Painter and D. G. Jagelman.) *Cancer*, 1985, **55**, 2001.

Adrenal adenocarcinomas: histologic grading and survival. (C. P. Karakousis *et al.*) *J. Surg. Oncol.* 1985, **29**, 105.

Adrenal pheochromocytoma: a clinicopathologic review of 60 cases. (L. J. Medeiros *et al.*) *Hum. Pathol.* 1985, **16**, 580.

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TECHNICAL DATA

DATA SHEET

PDS* (Polydioxanone) Sterilised Absorbable Synthetic Monofilament Suture

Presentation
PDS (Polydioxanone) Monofilament Synthetic Absorbable Suture is prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding D & C blue No 6 (gauge 0.2 metric and 0.3 metric) D&C violet No 2 (gauge 0.4 metric to 5 metric) during polymerisation. These sutures may also be manufactured undyed (clear).

PDS (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass.

Data obtained from implantation studies in rats show that, at two weeks post implantation, approximately 70% of the suture strength is retained whilst at four weeks the strength retention is approximately 50%. At eight weeks approximately 14% of the original strength remains. *This indicates a significantly longer period of wound support than previously available with an absorbable suture.*

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within six months.

Uses
PDS (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal mucosal sutures could cause localised irritation if left in place for longer than 10 days and should be removed as indicated. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption

The safety and effectiveness of PDS (Polydioxanone) sutures in neural and cardiovascular tissue have not yet been established. The use of this material in the renal tract is currently under investigation.

Pharmaceutical Precautions
Do not resterilise.

Legal Category P
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Packaging
The gauge range available will be 0.3 metric (9/0) to 5 metric (2). Various lengths of material attached to non traumatic stainless steel needles are packaged in sealed aluminium foil sachets.

The primary pack is sealed within a peel-apart secondary pouch and contained in a film-wrapped drawer style carton.

Further Information
So suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos PL 0508/0011 (dyed); PL 0508/0012 (clear).

Br Pat No 1 540 053.

Date of preparation of Data Sheet—September 1982
Revised 1/1985.

DATA SHEET

Coated VICRYL* (Polyglactin 910) Sterilised Absorbable Synthetic Braided Suture

Presentation

The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Suture may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses
Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissue under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 10 days and should be removed as indicated.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) Sutures in neural tissue and in cardio-vascular tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category P
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities
Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sales is 12 packs contained in a film wrapped drawer style carton.

Further Information
No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

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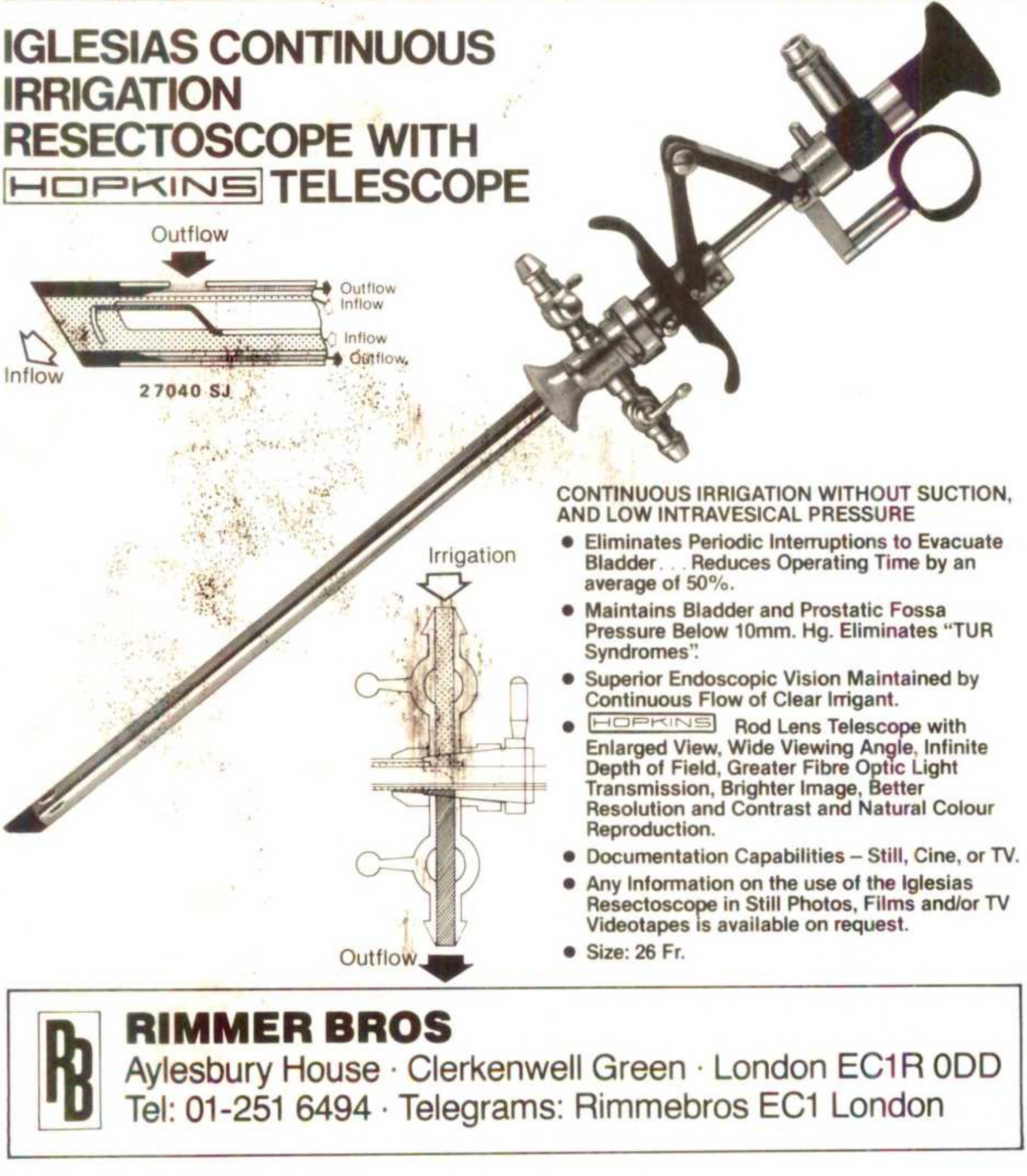

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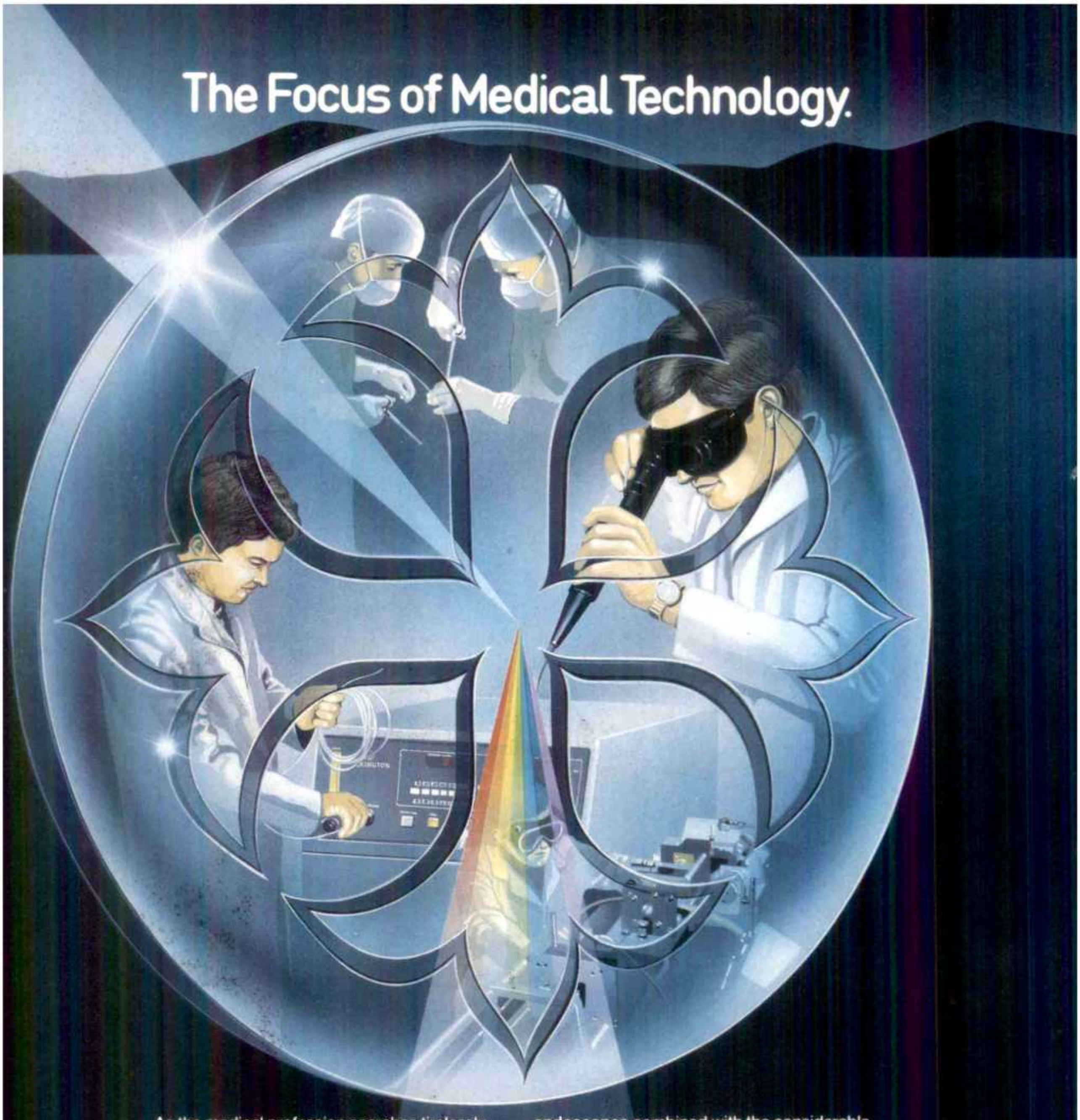

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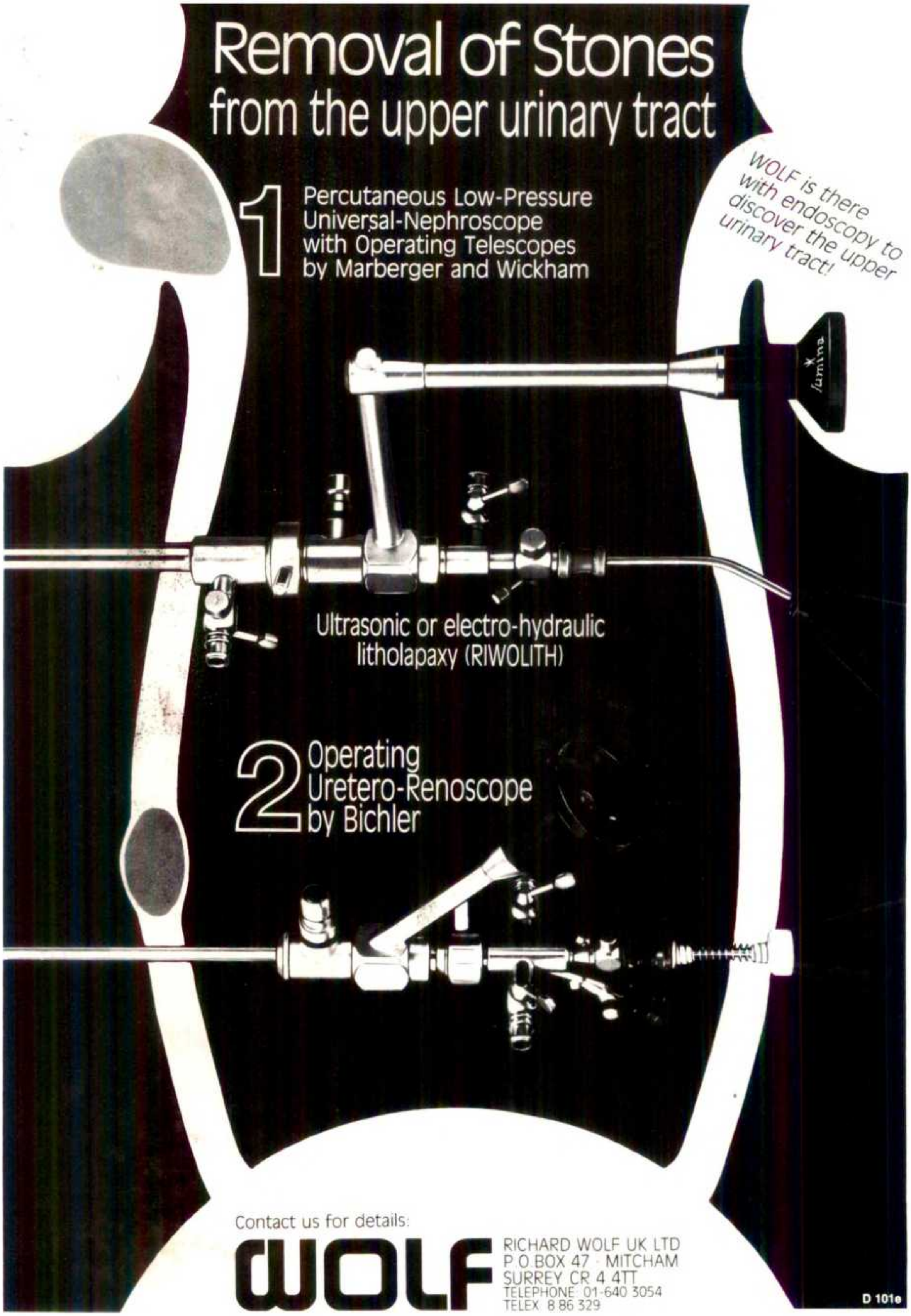

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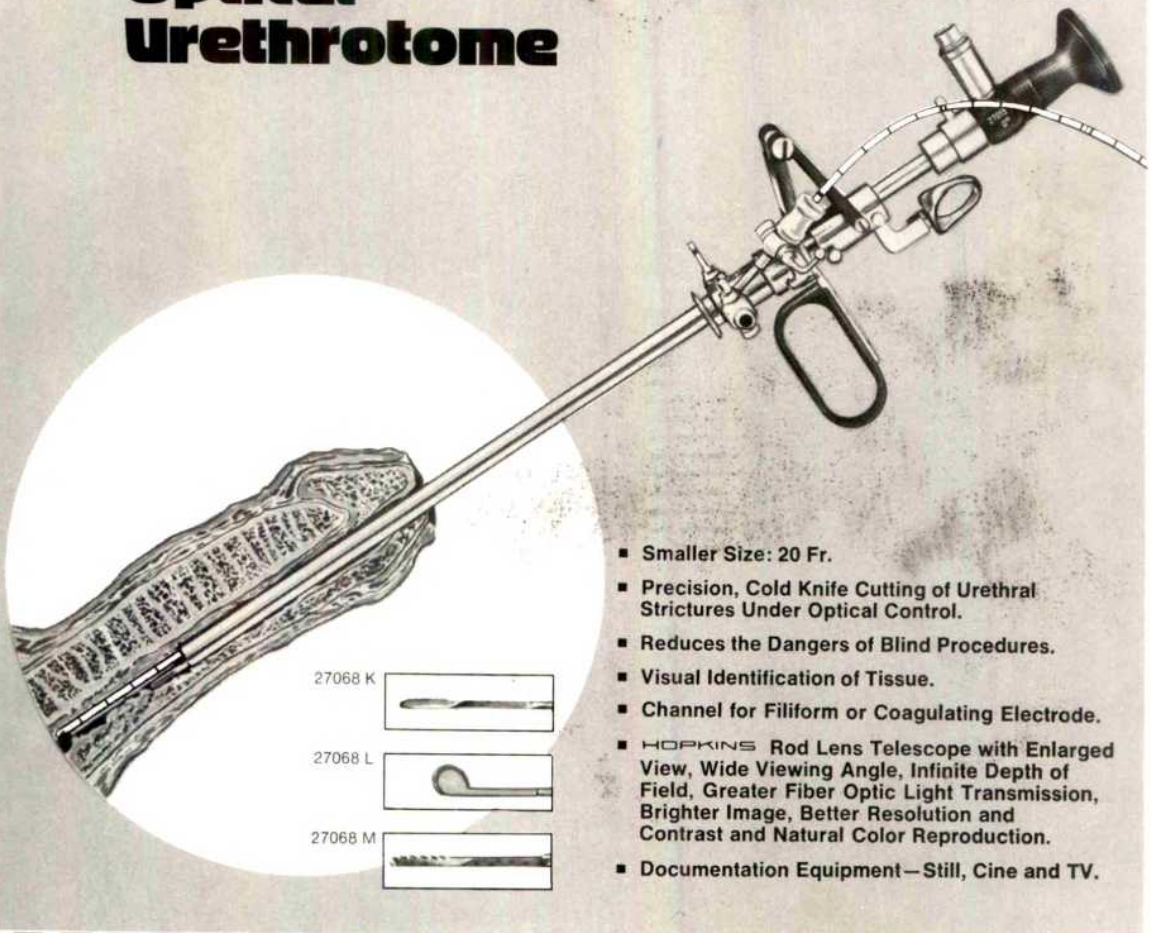

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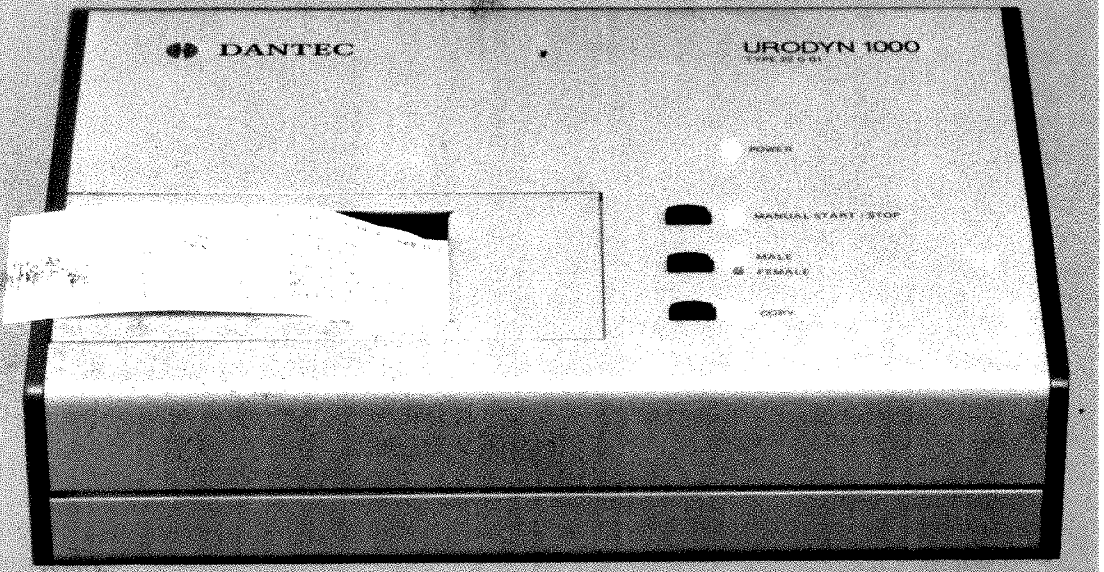

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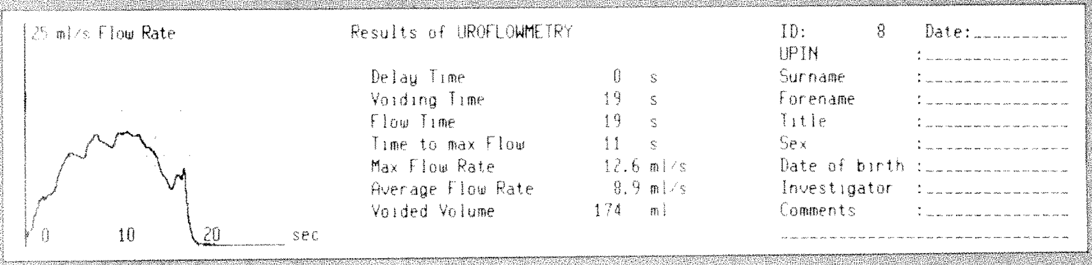
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Editors: N.J.R. George, J.A. Gosling, University of Manchester

Foreword by N.J. Blacklock

1986. 64 figures. Approx. 180 pages.
Hard cover DM 88,–
ISBN 3-540-15919-3

This book contains a full descriptive account of the important sensory disorders of the bladder and urethra: interstitial cystitis, the Urethral syndrome, and Prostatodynia. The authors' principle aim is to define these three entities concisely and to describe the investigational methods required to establish the relevant diagnosis.

Bladder Cancer

Editors: E.J. Zingg, Berne; D.M.A. Wallace, London

1985. 50 figures. XII, 301 pages.
(Clinical Practice in Urology)
Hard cover DM 170,–. ISBN 3-540-13239-2

"It aims to give a comprehensive review of bladder cancer, which it does in a compact and interesting manner. The histopathological and epidemiological aspects are included as well as the clinical aspects of the condition ... I would recommend it for all entrants to the urological field at senior house officer and registrar level."

W.G. Staff, British Journal of Hospital Medicine

Obstructive Uropathy

Editor: P.H. O'Reilly, Stockport

1985. 304 figures. XIV, 326 pages.
Hard cover DM 298,–. ISBN 3-540-15509-0

This is the first work to distill and update the subject of obstructive uropathy in one volume. It covers the investigation of all types of urinary tract obstruction by means of laboratory tests, radiology, ultrasound, CT scanning, antegrade pyelography and perfusion pressure flow studies, and the management of conditions encountered in clinical practice.

Incontinence

Editors: S.L. Stanton, London; E.A. Tanagho, San Francisco

Foreword by F. Hinman Jr.

2nd edition. 1986. Approx. 196 figures, approx. 11 tables. Approx. 300 pages.
Hard cover DM 160,–
ISBN 3-540-15821-9

From the reviews of the first edition:
"This book has two main strengths, first it aims to be as scientific as current knowledge allows and the editors have been successful in persuading the authors to write to a pattern... Secondly the book gives a comprehensive description of treatments available ... This book achieves its aims and gives a clear account of the application of recent knowledge to the treatment of women with incontinence of urine."

D. Warrell, British Journal of Obstetrics and Gynaecology

Percutaneous and Interventional Urology and Radiology

Editor: E.K. Lang, University of New Orleans

1986. 223 figures. Approx. 400 pages.
(Clinical Practice in Urology)
Hard cover DM 228,–. ISBN 3-540-15589-9

The latest volume in the "Clinical Practice in Urology" series provides comprehensive information on the interventional uroradiologic processes developed mainly during the last decade. Each topic is covered from the viewpoint of indications, technique, potential complications and their avoidance.
The book deals exclusively with uroradiology, rather than the entire field of interventional radiology, thereby offering a particularly valuable and in-depth guide.

Urodynamics
Upper and Lower Urinary Tract II

Editors: W. Lutzeyer, J. Hannappel, Technische Hochschule Aachen

1985. 243 figures, 22 tables. XI, 343 pages.
Hard cover DM 168,–
ISBN 3-540-15357-8

This volume reviews the essential results of clinical and research urodynamics during the past 12 years. It is based on a follow-up meeting held to review the development since the historical 1971 Aachen meeting. This follow-up review is preceded by reports from a special workshop on mycogenic control, hydrodynamics and mechanics of the upper urinary tract.

Urolithiasis: Etiology, Diagnosis

Edited by H.-J. Schneider, Giessen
With contributions by numerous experts
(Handbook of Urology, Vol. 17/1)

1985. 168 figures. XIII, 428 pages.
Hard cover DM 268,–
Reduced price for subscribers of the entire series: Hard cover DM 248,–
ISBN 3-540-15582-1

Urolithiasis: Therapy, Prevention

Edited by H.-J. Schneider, Giessen
With contributions by numerous experts
(Handbook of Urology, Vol. 17/2)

1986. Approx. 350 pages.
Hard cover DM 218,–
Reduced price for subscribers of the entire series: Hard cover DM 198,–
ISBN 3-540-15789-1

Urologists and nephrologists will welcome this fully comprehensive work in two independent volumes, presenting the current state of knowledge on urolithiasis etiology, diagnosis, therapy, operative treatment, and prevention.
Special emphasis is placed on the latest developments in the instrumentation and surgery of urolithiasis. The up-to-date methods of treatment are described by experts who initiated them.
The work covers world-wide research and the relevant literature, including the latest developments.

W. Leistenschneider, R. Nagel

Atlas of Prostatic Cytology
Techniques and Diagnosis

Foreword by G. Dhom
Translated from the German by R. Mills, D. Winter

1985. 325 color and black and white illustrations, 27 tables. X, 227 pages.
Hard cover DM 220,–. ISBN 3-540-13954

This monograph fulfills the double mission describing all tried and proven methods of cytological evaluation of the prostate know to date which are relevant for the clinic and independent practice, and of providing instruction in the basic techniques required for the application of this approach. The fu potential of prostatic cytology is clearly an impressively demonstrated.
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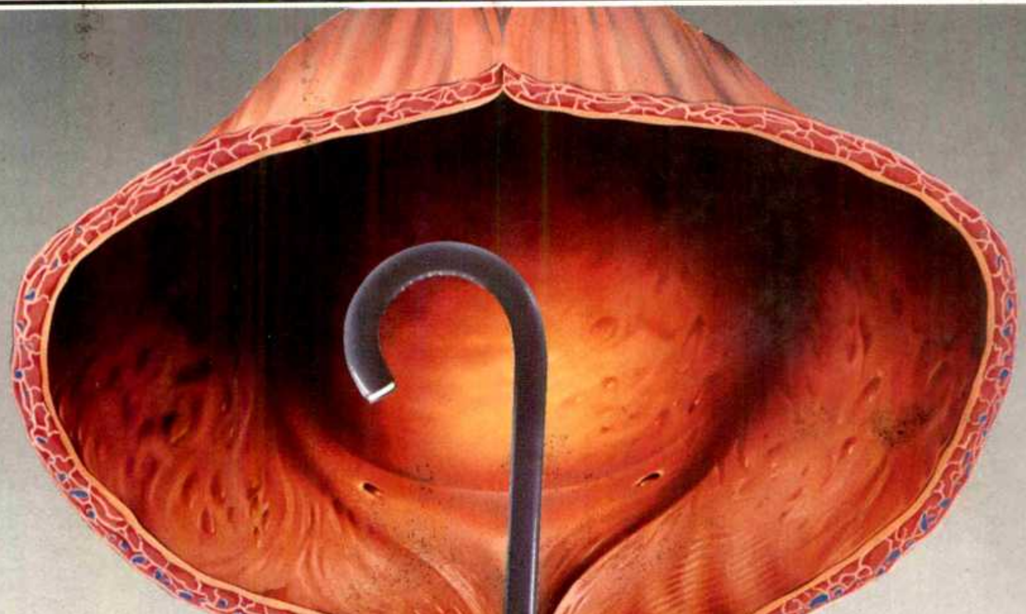

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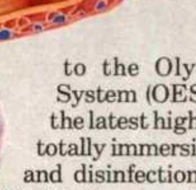
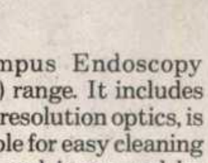


Retro view of the bladder neck



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British Journal of Urology (1986), **58**, 113-118

REVIEW

Priapism: a Three-phase Concept of Management According to Aetiology and Prognosis

J. POHL, B. POTT and G. KLEINHANS

Department of Urology, Münster University, Münster, Federal Republic of Germany

Summary—Priapism is a persistent, painful erection of the penis unassociated with sexual stimulation or desire, and detumescence does not occur following ejaculation. Prolonged pathological erections may occur and it is only when they are painful that the term priapism should be used. The erection is limited to the corpora cavernosa.

Although the syndrome was named after Priapos, the mythical Greek god of fertility, impotence persists in one half of patients treated for priapism. The disease is rare; the literature consists mainly of case reports and comprehensive reviews are seldom found. Permanent sequelae cause a psychological and physical handicap and justify the present review, which is based upon recent literature as well as personal clinical experience of 15 patients. We have reviewed 170 reports describing 1400 cases of priapism and have based the analysis upon the 230 single case reports found in the literature.

Aetiological Factors

Thirty-eight different aetiological factors are described in priapism. The relationship between the onset of priapism and perineal trauma, sickle cell disease, other rare types of anaemia, leukaemia, thrombo-embolic diseases as well as carcinoma of the penis or its neighbouring organs is recognised. Current interest focuses on the potential influence of the use and abuse of alcohol (Forssberg *et al.*, 1981), drugs causing psychic and physical dependence, antihypertensives, antidepressants and especially alpha-adreno-receptor blocking agents (Scher *et al.*, 1983). A relationship between these drugs and the development of priapism may exist, but is difficult to substantiate until the pathophysiology of priapism has been established.

The origin of one-third of all cases of priapism is unexplained or idiopathic (Table) and 21% were associated with drug therapy or alcohol abuse. Other important factors are perineal trauma (12%), sickle cell anaemia (11%) and inflammatory disorders of the urogenital tract (8%). The incidence of the different aetiological factors varies significantly amongst authors (Laroque and Cosgrove, 1974; Winter, 1978; Marx, 1981). The incidence of the aetiological factors at different ages reflects the incidence of age for the underlying disorder, *e.g.* sickle cell anaemia or trauma (Pohl *et al.*, 1984).

It is still not known why priapism is comparatively rare in such common disorders as hypertension, diabetes mellitus, inflammatory diseases of the urinary tract and ingestion of antidepressives, antihypertensives and anticoagulant drugs as well as alcohol.

Physiology of Erection

Erection, a physiological phenomenon, is caused by the interplay of haemodynamic, neurogenic and psychogenic factors. Essential requirements consist of intact erectile tissue, a normal vascular system and a delicate neurological mechanism. The tunica albuginea limits the maximal increase in size of the

Accepted for publication 9 December 1985

Table Aetiological Factors in 230 Patients with Priapism

	Aetiological factor	*Percentage*
Drug therapy	Antihypertensive agents	4
	Psychotropic agents	5
	Drug alcohol abuse	5
	Anticoagulants	6
	Other drugs	15
Trauma		12
Sickle cell disease		11
Leukaemia		6
Thrombo-embolic disorders		4
Other haematological disorders		2
Inflammation of urogenital tract		8
CNS/spinal cord disorders		3
Dialysis		2.5
Neoplasm		1
Idiopathic		35
Recurrent priapism		18
Multiple factors		12

penis and is responsible for the firmness of the erected penis.

In 1952 Conti stated a physiological concept of erection which has been accepted widely. He stated that shunting of arterial blood into the cavernous spaces was caused by active contraction of smooth muscles of cushions or "polsters" in the penile vessels. The lack of "polsters" in children, juveniles and some adults with normal erections could not be explained by Conti's theory. A new concept, based on electronmicroscopical examination of the cavernous tissue, suggests the active involvement of the intracavernous structures in the development of erection as well as at the beginning of detumescence (Hauri, 1981). Contraction of the trabecular muscles leads to relative enlargement of the cavernous spaces and allows rapid filling by arterial inflow. A simultaneous reduction of venous outflow is not essential. Erection occurs with an initial perfusion rate of 20 to 50 ml/min and is maintained by a flow of 12 ml/min (Newman and Northup, 1981). The role of "sphincter-like structures" of the vena penis profunda, located at the base of the penis (Casey and Woods, 1982) is not known. Artificial reduction of venous outflow by compression has never effected an erection but leads to penile oedema.

Pathophysiology of Priapism

Detumescence is also initiated by an active intracavernous mechanism consisting of an active contraction of the myofilaments which shorten the trabecular endothelium. The distance between the trabeculae is minimised, resulting in an active pumping out of the blood from the cavernous tissue. The arteriovenous anastomoses re-open when the rate of arterial blood flow decreases (Hauri, 1981).

A failure of detumescence to occur may be due to persistent increased arterial in-flow (high-flow priapism) on the basis of a disturbance in the neuro-arterial mechanism, or haemostasis (low-flow priapism) (Hauri, 1981).

In some patients a high arterial flow rate could be documented by cavernosography, angiography and Doppler flow studies. In comparison with the low-flow type of priapism, there is less penile firmness and the penis shows a livid discolouration. Pressure determinations during erection revealed that the intracavernous pressure may exceed the systolic blood pressure by a factor of 10; hence a vascular space may be temporarily separated from the main circulatory system (Meehan and Goldstein, 1983). The failure to reintegrate the cavernous space to the main circulatory system is characteristic of the low-flow type of priapism, and in these circumstances the penis is extremely hard and painful.

Therapy

The aim of therapy is to maintain erectile capacity and there are three phases of management. The treatment of priapism is symptomatic because little is known about the pathophysiology of the disorder.

Phase I

In the first phase of management, pain relief and sedation are accompanied by massive fluid transfusion and, if necessary, suprapubic bladder drainage and a reduction in blood pressure. This non-specific treatment may cause relief in the early phase of management and this is particularly so in those patients with repeated attacks of priapism (17%). At the same time it is obligatory to diagnose and treat any underlying causes. Such action may be curative of a secondary priapism. When a diagnosis of sickle cell anaemia is established, treatment is directed towards the disturbance in the microcirculation and a surgical procedure is performed for persistent priapism (Nelson and Winter, 1977; Adeyokunnu *et al.*, 1981). Leukaemia (Schreibman *et al.*, 1974) and other malignant tumours should be treated before giving specific treatment for the priapism. Thrombolytic and/or anticoagulant therapy is given only to those patients suffering from thrombosis of the pelvic veins or when the

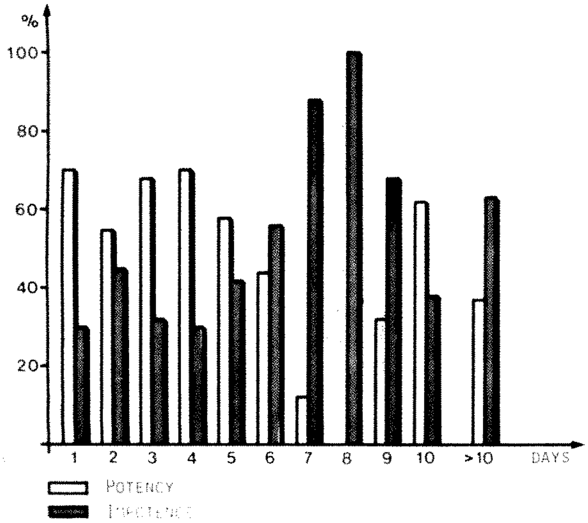

Fig. 1 Duration of priapism before treatment and the subsequent restoration of potency in 230 patients.

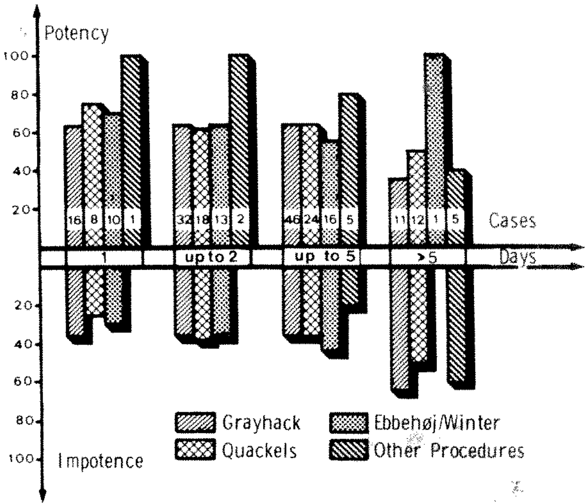

Fig. 2 Restoration of potency related to delay in treatment in 143 patients treated by operation.

priapism occurs during the course of a thromboembolic disorder (Marx, 1981).

The intake of alpha-adreno-receptor blocking agents should be discontinued as they may be responsible for the inhibited initiation of detumescence (Scher *et al.*, 1983). These, and other antihypertensive agents, may be replaced by nitroglycerine agents or nitroprusside agents as these induce smooth muscle relaxation and may have a beneficial influence on the intracavernous mechanism. Controlled hypotension is not generally accepted because of the risks and poor therapeutic success (Moloney and Sullivan, 1972; Bennet and Pilon, 1981).

In contrast to many opinions, we do not think that the interval between the onset of priapism and the initiation of specific treatment is of importance during the first 5 days. The incidence of impotence is not increased by such a delay (Figs 1 and 2). It is important to determine the type of priapism and penile perfusion by isotope phallography, angiography or Doppler sonography in all patients hospitalised within the first 3 days of the priapism. These investigations may provide further knowledge of the priapism syndrome and lead to the establishment of definite indications for the specific treatment described in the second phase of management.

Phase 2

The surgical treatment of priapism aims at establishing venous drainage from the corpora cavernosa into the unaffected corpus spongiosum (Quackels, 1964; Ebbehøj, 1975; Winter, 1976; Al-Ghorab, 1981), the long saphenous vein (Grayhack *et al.*, 1964), a dorsal vein of the penis (Barry, 1976) or into one of the lower arm veins (Ten Cate *et al.*, 1975).

The creation of a cavernous-glandular shunt (Ebbehøj, 1975; Winter, 1976; Al-Ghorab, 1981) is the treatment of choice because of its simplicity, adequate incidence of success (Fig. 3) and low incidence of complications (Pohl *et al.*, 1985). When two such operations fail to control the priapism, then an alternative procedure (Grayhack *et al.*, 1964; Quackels, 1964) should be performed. There have been rare clinical reports of the Barry (1976) and Ten Cate *et al.* (1975) procedures and there are a few positive reports of embolisation of the internal pudendal artery (Wear *et al.*, 1977). Complications are most common in the early post-operative period. In terms of prognosis, the extent of total induration, early shunt obliteration, urethral and transcutaneous fistulae as well as gangrene of the penis are of importance (Pohl *et al.*, 1985).

Phase 3

The aim of post-operative care and rehabilitation is to restore erectile potency. The first and often incomplete erection should occur not later than 3 months after treatment. Persistent impotence or impaired potency should be investigated by cavernosography, which provides detailed information about the trabecular system and the existence of open shunts, ligation of which may restore potency

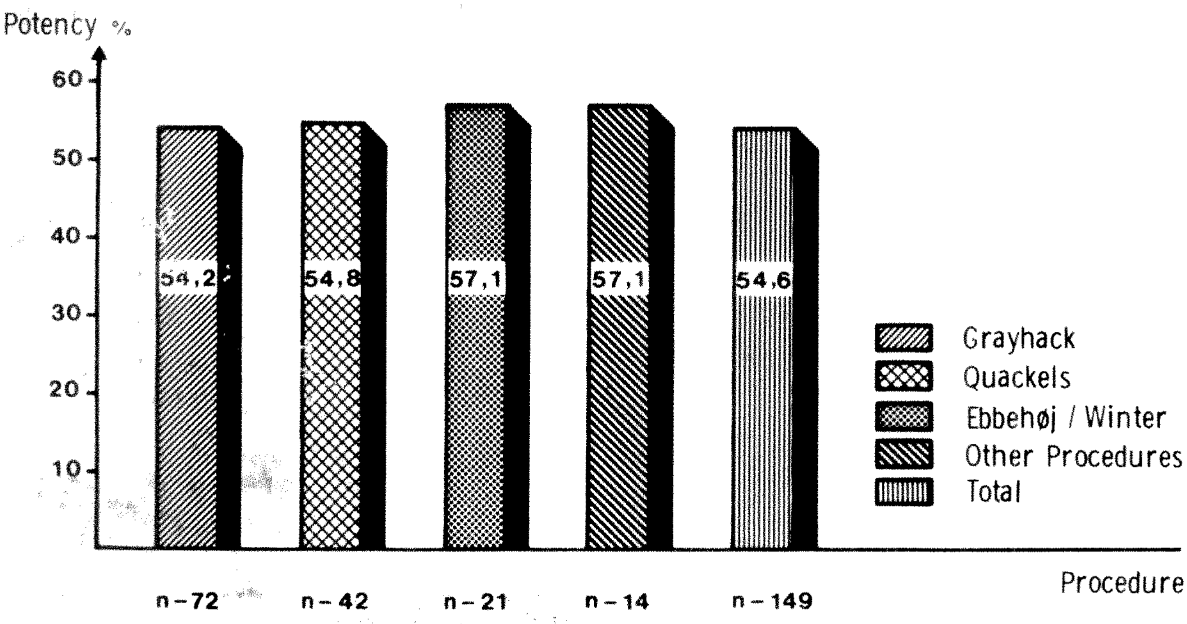

Fig. 3 Post-operative success rate in restoring potency after various operative procedures in 149 men.

even after several years (Hauri, 1981; Müller *et al.*, 1984). In patients with irreversible fibrosis of the corpora cavernosa, documented by a honeycombed appearance at cavernosography and without passage of contrast to the deep venous plexus, implantation of the penile prosthesis is indicated. Arterial occlusion, documented by angiography, is often seen when cavernosography did not reveal any abnormality. If there are no other vascular lesions, or if the vascular system is minimally affected, then revascularisation may be done, although the results of long-term follow-up have not been promising (Hawathmeh *et al.*, 1982). Persistent pressure and flow rates seem to be responsible for the fibrotic organisation of the cavernous structures. In some patients the intracavernous injection of papaverine and phentolamine (chemical prosthesis) by the patient himself is an alternative to the penile implant (Zorgniotti and Lefleur, 1985).

Prognosis

Hinman (1960) in his classic paper on priapism stated "treatment is generally not effective, impotency is the usual result". It is difficult to assess the results of treatment and the average duration of follow-up is often short (Klein *et al.*, 1972), but with the introduction of the operative shunt procedures more than 50% of patients remain potent. The fact that success occurs in 55% of patients, and is independent of the type of venous shunt operation, leads to the conclusion that the aetiology and pathophysiology of the condition determine the prognosis and that unknown pre-therapeutic factors have a greater influence than the therapeutic procedure itself.

The age distribution of the 230 patients with priapism is shown in Figure 4 and the maintenance of potency after priapism is much greater in the younger age groups (Fig. 5). This may be due to the reduced frequency of coitus that occurs in older men (Fig. 6). The age factor may limit the success

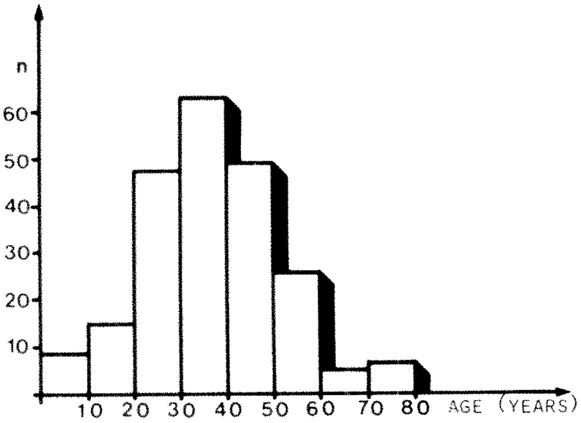

Fig. 4 Age distribution of 230 patients with priapism.

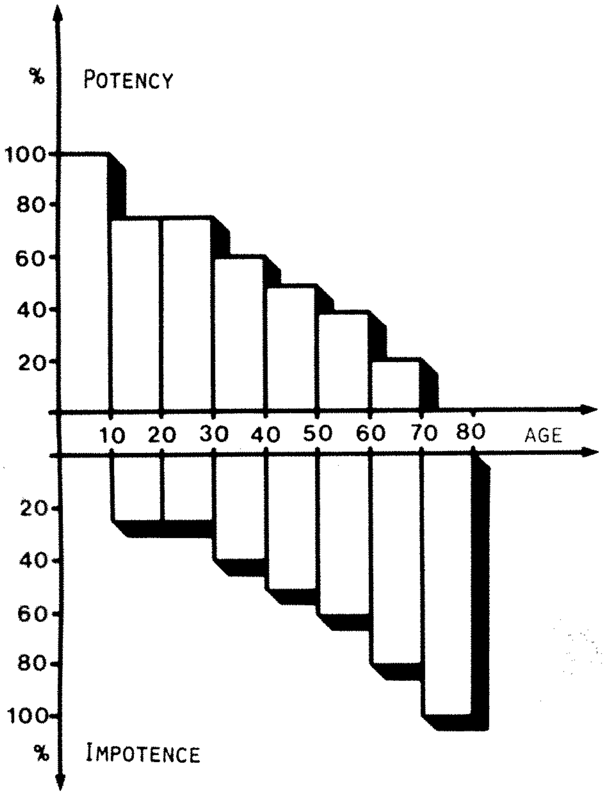

Fig. 5 Restoration of potency according to the age of the patient.

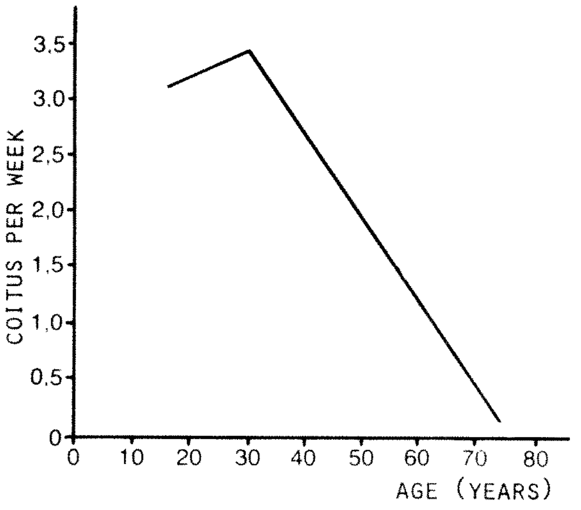

Fig. 6 Age and frequency of intercourse (Kinsey's modification).

rate of all forms of treatment and the degree of pretherapeutic potency is of great importance.

Differences in the prognosis of priapism associated with different aetiological factors are based upon age (Pohl *et al.*, 1984). Priapism of traumatic aetiology has a good prognosis (80% regain potency) and is explained by the high incidence of patients aged 20 to 30 years. Patients with sickle cell anaemia are young and have a good prognosis, whereas patients with a history of antihypertensive therapy are older and have a bad prognosis with regard to potency.

Most authors declare priapism to be an emergency and demand an immediate specific therapy, usually in the form of a venous shunt operation, although there is no good statistical evidence for this view. The contrary opinion (Laroque and Cosgrove, 1974; Marx, 1981) led us to examine the prognosis for each of the first 5 days of duration of priapism and we found the maintenance of potency to be 65% (Figs 1 and 2). It was surprising to find that even when the intervention was performed more than 10 days after the onset, 40% of the men were reported to be potent. Hence a delay in the initiation of specific therapy is justified and the patient may be fully investigated. It is remarkable that patients who had suffered from previous episodes of priapism with spontaneous relief had a good prognosis (Pohl *et al.*, 1984).

It might be argued that better results may be achieved when therapy is initiated after a couple of hours. This argument cannot be accepted because the therapeutic results of tests on the first day are no better than those on the following 4 days (Fig. 1).

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The Authors

J. Pohl, MD, Urologist.
B. Pott, MD, Resident.
G. Kleinhans, MD, Urologist.

Requests for reprints to: J. Pohl, Urologischen Klinik und Poliklinik, Zentralklinikum der WWU, Albert-Schweitzer-Str. 33, D-4400 Münster, Federal Republic of Germany.

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Renal Function Following Surgical Correction of Vesico-ureteric Reflux in Childhood

D. J. SCOTT, H. N. BLACKFORD, M. R. L. JOYCE, A. R. MUNDY, C. H. KINDER, G. B. HAYCOCK and C. CHANTLER

Departments of Paediatric Nephrology and Urology, Guy's Hospital, London

Summary—To assess the effectiveness of the surgical correction of vesico-ureteric reflux, current renal function was determined in 56 children with scarred kidneys who had undergone ureteric reimplantation between 1978 and 1983. The children were aged between 2 and 15 years, had no coexisting urological disease and a glomerular filtration rate (GFR) of <90 ml/min/1.73 m^2. In the 32 patients who had bilateral reimplantation of ureters draining bilaterally scarred kidneys the improvement in GFR following surgery was highly significant ($P<0.001$), with improvement occurring in 75%. The greatest improvement was in patients where the GFR was <50 ml/min/1.73 m^2 (29%). Individual kidney GFR was estimated in 42 kidneys and 81% improved after surgery. This improvement was highly significant ($P<0.001$).

The treatment of children with severe vesico-ureteric reflux (VUR) remains controversial and the indications for operation are still unclear. In the past 5 years several attempts have been made to clarify the situation (Lyon *et al.*, 1980; Birmingham Reflux Study Group, 1983) and a prospective international study is in progress to answer the question (International Reflux Study Committee, 1981). Dunn and Smith (1982) demonstrated poor results following conservative treatment of children with severe (grade 3) reflux. The Birmingham Reflux Study Group (1983), in an interim report on their prospective trial, found no short-term benefit from surgery, when compared with conservative management.

The long-term results of surgery are known to be beneficial in that reflux is usually cured (Carpentier *et al.*, 1982), renal and physical growth occurs (McRae *et al.*, 1974; Atwell and Vijay, 1978; Merrell and Mowad, 1979; Bauer *et al.*, 1980; Carson *et al.*, 1982) and a preliminary study demonstrated improvement in total renal function (Mundy *et al.*, 1981). Conservative management with the meticulous prevention of infection with prophylactic antibiotics was associated with normal renal growth (Smellie *et al.*, 1981), whereas scarred kidneys associated with persisting VUR grew poorly when infections were treated but not prevented (Cardiff—Oxford Bacteriuria Study Group, 1978).

This study reports the changes in renal function following anti-reflux surgery in patients at this hospital.

Patients and Methods

Between January 1978 and February 1983, 59 children underwent surgical correction of VUR and fulfilled the criteria for entry into the study. Analysis was limited to children aged between 2 and 15 years. Children under the age of 2 were excluded because a physiological increase in GFR is known to occur in this age group (McCrory, 1972). Children with coexisting urological disease (*e.g.* urethral valves, neuropathic bladder) were excluded and analysis was limited to children who had a total GFR <90 ml/min/1.73 m^2 either at operation or at subsequent follow-up. Particular care was taken to include those patients who had a GFR >90 initially and whose GFR subsequently fell, so that

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Read at the 40th Annual Meeting of the British Association of Urological Surgeons in Dublin, July 1984 results would not be biased in favour of operative treatment. The minimum follow-up period was 6 months and in all patients reimplantation was by the Cohen advancement technique (Cohen, 1975). Children who experienced complications post-operatively were included in the analysis.

The study was conducted retrospectively. Pre-operative data were obtained from case notes and post-operative data either from the case notes (8 patients) or at a follow-up appointment when current renal function was determined (48 patients). Patients brought back for determination of their current renal function were measured using a Holtain Stadiometer, had their blood pressure recorded, urine cultured and a serum creatinine estimation performed. If a ^{99m}Tc-dimercapto-succinic acid (DMSA) renal scan and a ^{51}chromium-edetic acid (^{51}Cr-EDTA) clearance had been performed pre-operatively, these were repeated. Three patients had inadequate post-operative data in their case notes and follow-up data could not be obtained. In two cases the children had moved abroad and could not be traced and the third declined to attend the follow-up appointment. These children were excluded from the study.

Renal excretory function was assessed using the height/plasma creatinine formula (Morris *et al.*, 1982). Those who had ^{51}Cr-EDTA clearance performed pre-operatively also had renal function assessed by this method (Chantler and Barratt, 1972).

Individual renal function was obtained pre-operatively from either a DMSA renal scan or from a ^{99m}Tc-diethylene-triamine-pentacetic acid (DTPA) renal scan. Post-operative split function was estimated using DMSA renal scans, as it has been shown that divided DMSA uptake is more accurate when determining split function (Bingham *et al.*, 1978). Oblique views were obtained to assess the presence of renal scarring.

The classification of patients fulfilling the study criteria is shown in Table 1. There were 37 girls and 19 boys with a mean age of 7.3 years (range 2.1-14.0). Mean duration of follow-up was 2.7 years. Assessment of individual kidney function was limited to kidneys with scarring demonstrated either on intravenous urography or DMSA renal scan. Analysis of results in all cases was by the paired *t* test.

Table 1 Classification of Patients (n = 56)

Group	*Operation*	*Renal scarring*	*No.*
A	Bilateral reimplantation	Bilateral	32
B	Bilateral reimplantation	Unilateral	7
C	Unilateral reimplantation	Unilateral	8
D	Unilateral reimplantation + nephro-ureterectomy	Bilateral	5
E	Unilateral reimplantation + transuretero-ureterostomy	Bilateral	4

Results

The total GFR, estimated by the height/creatinine formula, is shown for the five groups of patients in Table 2. The largest group consisted of patients who had bilateral reimplantation of bilaterally scarred kidneys (group A) and in this group the improvement in renal function was highly significant ($P<0.001$). The individual results in group A can be seen in Figure 1, which shows that improvement occurred in 75%. Sequential analysis, excluding patients with a GFR >80, then >70 and so on, showed that the most significant improvement occurred when the total GFR was <50 ml/min/1.73 m^2. The percentage improvement in this group was 29% (Figs 2 and 3). Patients with a total GFR <30 ml/min/1.73 m^2 showed a percentage fall of 12%, though this was not of statistical significance. To ensure that the results were not biased by the inclusion of patients whose post-operative GFR was falsely high, the results in group A were re-analysed, excluding cases where the post-operative GFR was >90 ml/min/1.73 m^2. The improvement in GFR was still statistically significant ($P<0.001$).

Table 2 Change in Total GFR Following Surgery

		Total GFR			
Group	*No.*	*Pre-op*	*Post-op*	*t*	*P*
A	32	61.2 ± 15.5	71.2 ± 19.6	4.183	<0.001
B	7	73.3 ± 12.2	79.9 ± 6.5	1.610	<0.5
C	8	69.0 ± 24.8	78.1 ± 30.5	1.887	<0.5
D	5	64.6 ± 12.2	61.0 ± 14.8	−0.937	<0.5
E	4	28.9 ± 8.5	31.6 ± 12.3	1.044	<0.5

Analysis of renal function in patients in groups B, C, D and E showed no significant change following surgery.

Individual kidney GFR was determined both pre- and post-operatively by DMSA renal scan in 35 patients, so that in 60 kidneys the change in GFR following surgery could be determined. In six patients the pre-operative split function was estimated by a DTPA renal scan and in these patients

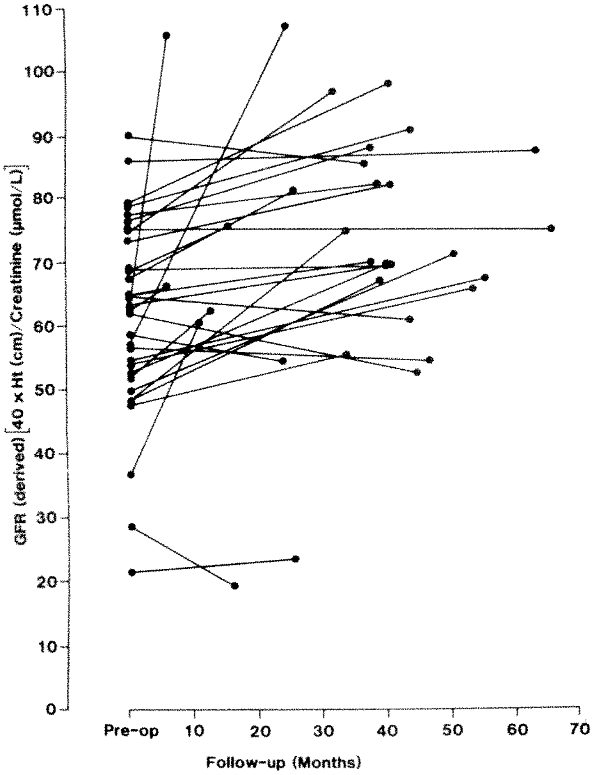

Fig. 1 Change in GFR in patients following bilateral reimplantation of bilaterally scarred kidneys (group A).

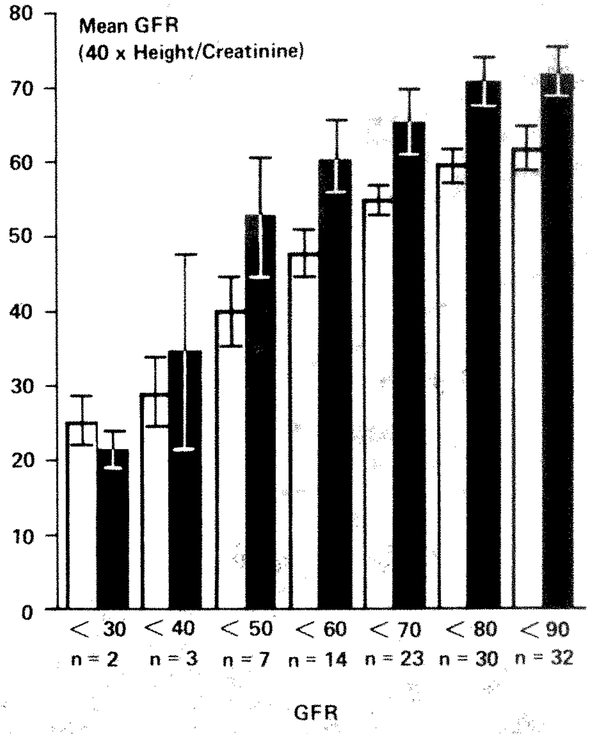

Fig. 2 Sequential analysis of the mean GFR in Group A (together with the standard error of the mean (SEM) in each group).

reimplantation of eight scarred kidneys was performed. Classification of kidneys was according to groups A to E (Table 3). The change in renal function in these groups is shown in Table 4. The only significant improvement was in group A. Analysis of the change in individual kidney function following simple reflux-preventing surgery (groups A-E) showed highly statistically significant improvement at the 0.1% level ($t=4.912$). Improvement occurred in 42 of 52 kidneys (81%) (Fig. 4). Sequential analysis, excluding those kidneys with a GFR <60, <50 and so on, showed that there was no improvement in kidneys with a GFR <30 ml/min/1.73 m^2 (Fig. 5).

In patients where the GFR was measured by both the ^{51}Cr-EDTA clearance and the height-creatinine formula, the correlation between measured and estimated GFR was 0.87, excluding cases with a GFR >90 ml/min/1.73 m^2. Total GFR measured by EDTA clearace was available in 12 patients and in 11 it was possible to obtain the individual kidney function from DMSA renal scan. Results again demonstrated statistically significant improvement (Table 5).

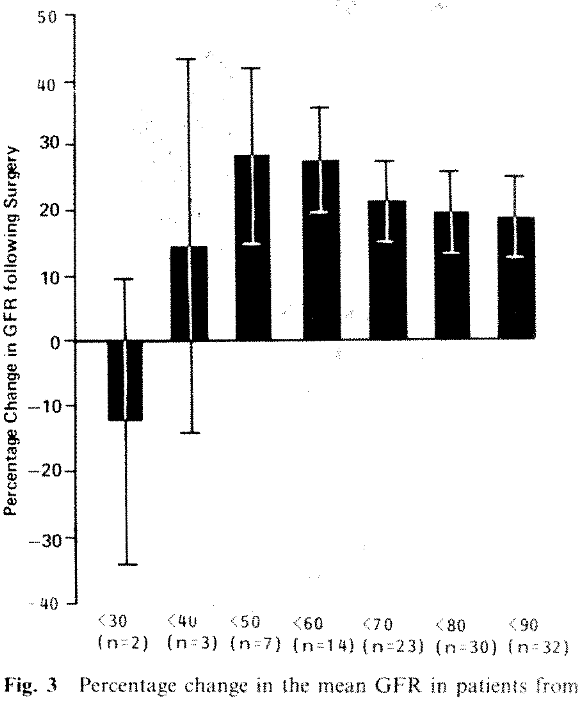

Fig. 3 Percentage change in the mean GFR in patients from Group A, together with the SEM in each subgroup.

Table 3 Identification of Refluxing Units (n = 68)

	DMSA		*DTPA*	
Group	*Patients*	*Kidneys*	*Patients*	*Kidneys*
A	21	42	2	4
B	3	3	1	1
C	3	3	2	2
D	4	4	1	1
E	4	8	—	—
Total	35	60	6	8

Table 4 Change in Individual Kidney GFR Determined by DMSA Renal Scan Following Reflux Corrective Surgery

		GFR			
Group	*No.*	*Pre-op*	*Post-op*	*t*	*P*
A	42	29.3 ± 12.6	35.5 ± 15.5	5.884	<0.001
B	3	21.3 ± 10.6	16.1 ± 8.0	1.883	<0.5
C	3	25.5 ± 6.7	33.8 ± 13.5	1.618	<0.5
D	4	61.2 ± 11.8	59.4 ± 16.5	2.595	<0.1
E	8	14.5 ± 6.3	15.8 ± 9.9	0.682	ns

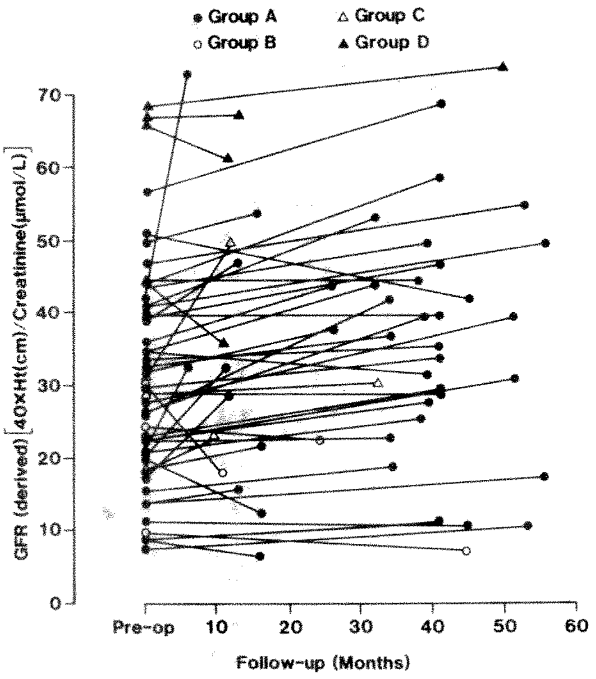

Fig. 4 Change in the GFR of scarred kidneys following ureteric reimplantation (Groups A-D).

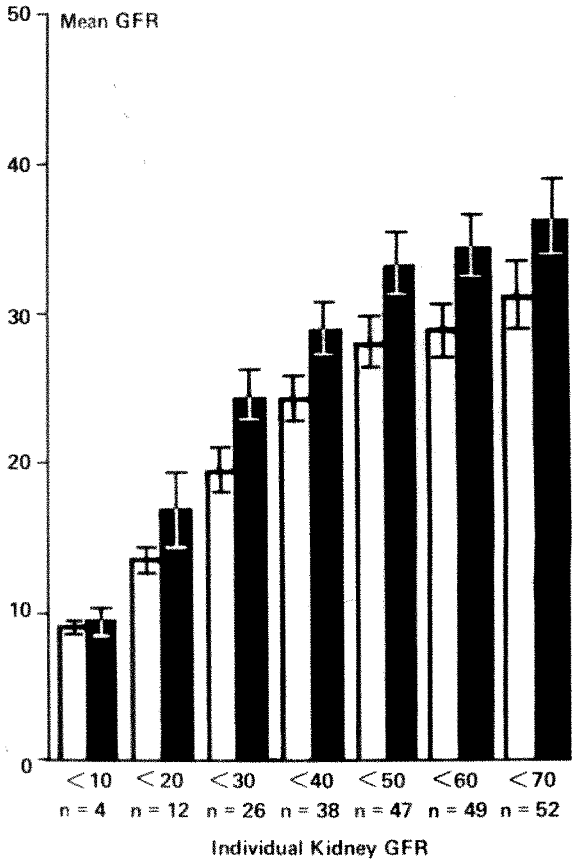

Fig. 5 Sequential analysis of the individual kidney GFR following reflux-preventing surgery (Groups A-D) togerther with SEM.

The renal function of the four children who underwent complex reflux-preventing surgery (group E) is shown in Table 6.

Overall, following surgery, reflux was cured in 93% of cases. In two patients (3.5%) the reflux was still present post-operatively but was reduced in degree. This eventually resolved spontaneously. In a further two patients (three ureters) there was post-

Table 5 Renal Function in 12 Patients Determined From ^{51}Cr-EDTA Clearance

		Total GFR		
No.	Pre-op	Post-op	t	*P*
12	70.2 ± 19.4	77.1 ± 22.2	2.140	<0.1
		Individual kidney GFR		
No.	Pre-op	Post-op	t	*P*
22	39.3 ± 19.3	42.7 ± 23.2	2.860	<0.01

Table 6 Change in GFR Following Unilateral Reimplantation and Transuretero-ureterostomy

	Pre-op	*Post-op*	*t*	*P*
Total GFR (n = 4)	28.9 ± 8.5	31.6 ± 12.3	1.044	<0.5
Individual kidney GFR (n = 8)	14.46 ± 6.33	15.79 ± 9.91	0.682	ns

operative vesico-ureteric junction obstruction, which in two cases required re-operation to achieve a successful result.

The incidence of hypertension in the children studied was 14.3% and a comparison of DMSA scans before and after surgery showed that no new scars had developed.

Discussion

These results demonstrate that renal function (GFR) improves after surgical correction of vesico-ureteric reflux and that the improvement is greatest in those kidneys that have not been severely damaged (GFR >30 ml/min/1.73 m^2). Severely damaged kidneys (split function <15%) have a growth potential (Carson *et al.*, 1982) and whether these small kidneys should be removed is a controversial point. Our current policy is to remove them because of the risk of hypertension, but it is of note that, whilst the change was not of statistical significance, the only group of children who had reduced function post-operatively were those who underwent nephro-ureterectomy of a contralateral small kidney (group D). It could be argued that these kidneys shoud be retained and their ureters reimplanted, as suggested by Bauer *et al.* (1980).

Long-term follow-up of children with scarred kidneys is important because of the risk of hypertension (Wallace *et al.*, 1978). Our study confirms this and it is noteworthy that two children with undetected hypertension were discovered as a result of the follow-up study.

Surgical correction of vesico-ureteric reflux does not obviate the need for long-term follow-up, since children with scarred kidneys remain at risk of developing hypertension. Reflux surgery minimises the risk of further renal damage from the combined effects of infection and continuing reflux.

While we, like others (Carpentier *et al.*, 1982), have shown that for children with scarred kidneys surgical correction of vesico-ureteric reflux is effective and the complication rate low, it may be that conservative management of these children would have produced similar results.

Our results do not reveal at what stage after surgery improvement in renal function occurs, though Figure 1 suggests that it occurs shortly after surgery. It is hoped that the prospective study currently in progress will answer these questions (International Reflux Study Committee, 1981).

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The Authors

D. J. Scott, MRCP, Research Fellow in Paediatrics.
H. N. Blackford, MSc, FRCS, Senior Registrar in Urology.
M. R. L. Joyce, FRCS, Consultant Urological Surgeon.
A. R. Mundy, MS, FRCS, MRCP, Senior Lecturer in Urology.
C. H. Kinder, MChir, FRCS, Consultant Urological Surgeon.
G. B. Haycock, MD, FRCP, Consultant Paediatric Nephrologist.
C. Chantler, MD, FRCP, Professor of Paediatric Nephrology.

Requests for reprints to: C. Chantler, Department of Paediatrics, Guy's Hospital, St Thomas Street, London SE1 9RT.

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Dose Titration in Clinical Trials
An Example Using Emepronium Carrageenate in Detrusor Instability

J. A. MASSEY and P. ABRAMS

Clinical Investigation Unit, Ham Green Hospital, Bristol

Summary—Seventy-two women with proven detrusor instability completed a novel clinical trial of the new anticholinergic emepronium carrageenate (Cetiprin novum), which allowed for dose titration. The tolerated dose has been shown to correlate with the severity of symptoms. Statistically significant improvement was achieved in symptomatic and urodynamic parameters without serious side effects.

It is usual clinical practice to tailor treatment to the needs of the individual. The bioavailability of drugs may vary widely with weight, diet, constipation, etc., as well as with genetic factors (George, 1984; Parke, 1984). Parke concluded that incorrect dosage was the commonest cause of adverse side effects. When evaluating a new compound, therefore, it seems desirable to titrate doses individually.

This objective is essential in assessing anticholinergic therapy, where side effects are often the limiting factor to compliance and benefit. Emepronium, a quaternary ammonium compound, widely used as emepronium bromide, has not escaped this problem. An eightfold variation in its absorption has been demonstrated (Sundwall *et al.*, 1973). Concern over reports of oesophageal damage (Kavin, 1977) prompted the development of emepronium carrageenate, in which the active principle is released only in the presence of excess hydrogen or sodium ions. This new compound was tested in a unique titrated trial.

Patients and Methods

Seventy-two symptomatic women (aged 19–71 years; mean 44) underwent standard, medium-fill, water cystometry with regular provocation to confirm detrusor instability. Patients with bacteriuria or on medication likely to affect the urinary tract, such as beta blockers and diuretics, were excluded. A 5-day urinary diary, recording volume, urgency and episodes of incontinence, was completed before or at least 1 week after this examination.

The flow diagram for this titrated, double-blind, placebo-controlled, randomised cross-over trial is shown in Figure 1. All patients took 2½ tablets qid at all stages. The titration period was 1 week at 1600 mg/day. Treatment order was randomised into the groups shown between placebo and low (1200 mg/day), medium (1600 mg/day) or high (2000 mg/day) doses. Frequency/volume charts were kept for the final 5 days of each treatment period, which lasted 28 days. Urodynamic studies were repeated on the last day of each treatment. Blood and urine samples were analysed for drug levels as well as routine screening procedures.

The "instability index" was derived by summing the heights of all unstable waves and dividing by the cystometric capacity. Otherwise the terms used in this study conform to the recommendations of the International Continence Society (1984). To evaluate differences between treatments, analysis of variance after Hills and Armitage (1979) was used.

Results

Twenty-four patients entered the low dose and 43

Based on a Poster Demonstration at the Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

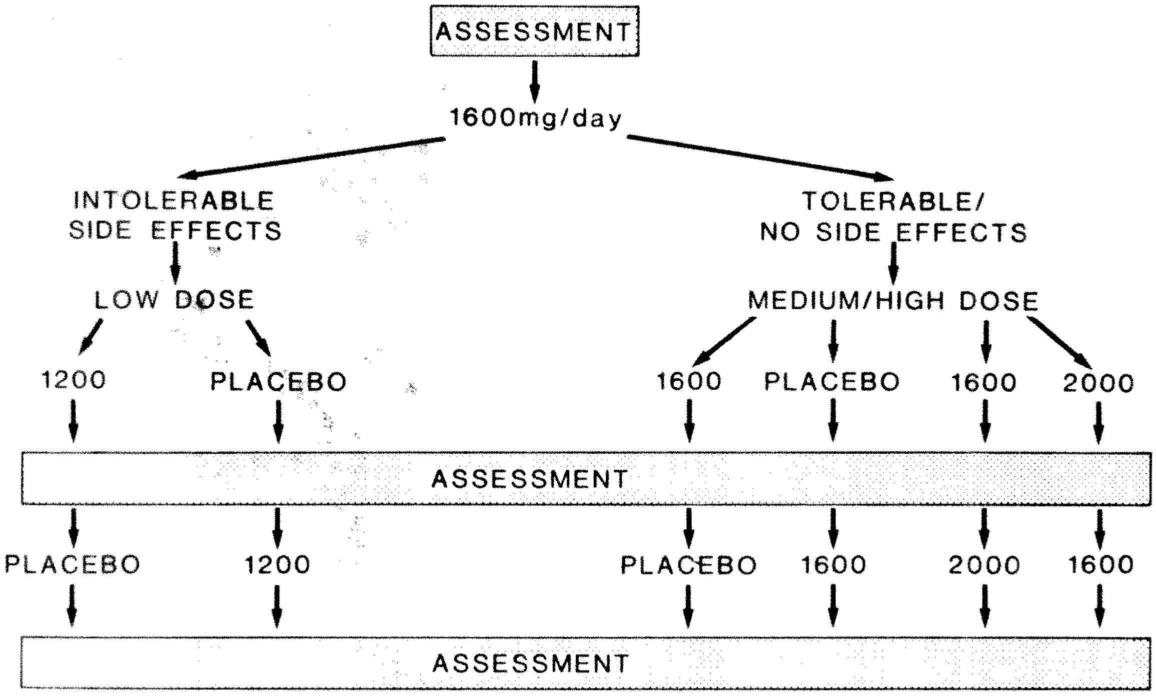

Fig. 1 Titrated trial flow diagram.

patients the medium or high dose arm of the study. Five patients were withdrawn during the titration phase.

The results are summarised in histogram form (Figs 2 and 3). All data showed the same trend towards improvement, with statistical significance at the 5% level or better for the micturition parameters of voids/day, urgent episodes/day and episodes of incontinence/day. This level was also reached in the urodynamic studies for first desire to void (FDV), "instability index", maximum cystometric capacity (MCC) and volume voided. No significant increase in residual urine was observed, all being below 50 ml. In the low dose group 50% of patients became stable on treatment, whereas none did on placebo. Similarly, in the medium/high dose groups together, 80% remained unstable on placebo, 71% after 1600 mg and only 55% after 2000 mg.

There were no cases of oesophagitis. One patient complained of mild retrosternal discomfort (on 1600 mg) but endoscopy within 24 h revealed a previously undiagnosed hiatus hernia without inflammatory changes. There were withdrawals for other reasons (Table 1). All but one placebo withdrawal occurred in the low dose study, giving a significant preponderance of patients with poorest tolerance of side effects in this group. Comparison of entry data between this and the medium/high dose group showed significant differences in symptomatic and cystometric variables (Table 2). All parameters tended to be less severe in the low dose group.

Although there was a rise in serum creatinine on treatment, all values remained within the normal range (Ryd-Kjellen *et al.*, 1973). In two patients serum alanine transaminase and serum aspartate transaminase levels rose above normal (see below). Otherwise no biochemical changes were seen.

There was a linear relationship between dosage and mean serum blood levels taken approximately 3 h after the last dose. The mean values were 63 μg/l (1200 mg), 144 μg/l (1600 mg) and 217 μg/l (2000 mg). The latter corresponds to an intramuscular dose of 25/50 mg and is higher than that recorded for emepronium bromide 800 mg/day (Meyhoff and Nordling, 1981), although sampled on average sooner after ingestion than in that study.

Discussion

Entry criteria for this study were rigorous and compliance surprisingly good considering the number of tablets taken per day, the completion of record forms and the repeated urine, blood and urodynamic studies. Acceptability of the drug by patients was high and their overall impression favourable, with improvement claimed most frequently by the

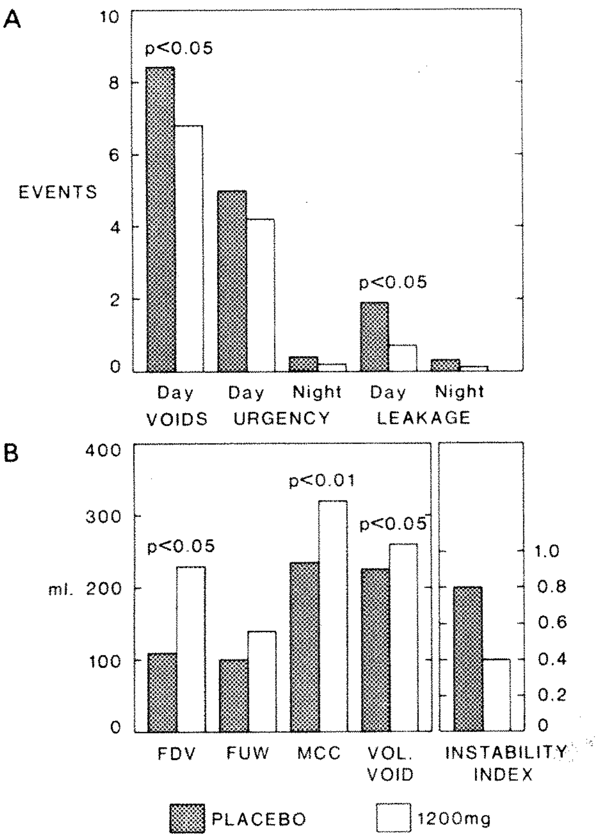

Fig. 2 Low dose group results (mean values). (A) micturition parameters. (B) urodynamic parameters.

drug-treated patients. There is a tendency for all symptoms, especially incontinence, to improve with increasing dosage of emepronium carrageenate.

Urodynamic data give a clearer picture of change with increasing dosage. All parameters were improved at 2000 mg/day. There were increases in volumes at first desire to void and at the occurrence of the first unstable wave (FUW) and a decrease in the "instability index". The maximum cystometric capacity increased with increasing dosage, mirroring the change in voided volume seen on the frequency/volume charts. Voiding parameters were unchanged except for an insignificant rise in the residual urine volume.

Cetiprin novum was well tolerated and without oesophageal side effects, even in one patient who took 50 tablets as a suicide attempt and developed only a moderate tachycardia. Changes in biochemistry were noted in two patients but further investigations suggested idiosyncrasy or an intercurrent viral illness. Neither patient was withdrawn from the study.

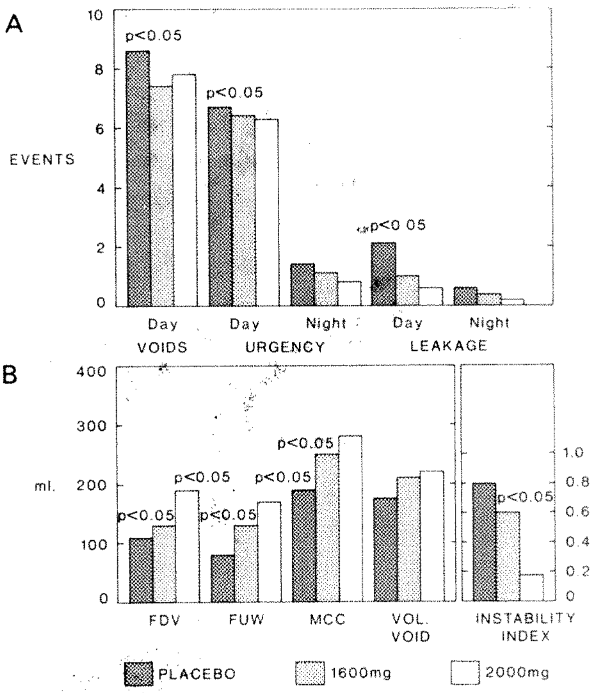

Fig. 3 Medium/high dose group results (mean values). (A) micturition parameters. (B) urodynamic parameters.

Table 1 Details of Patient Withdrawals

Indication	*No.*
Allergic skin reaction (titration phase)	2
Dry mouth, nausea, abdominal colic	8
Blurred vision	4
Placebo (various inc. dry mouth)	5
Intercurrent illness, non-attenders	5
Total	24

Table 2 Comparison of Entry Data for Low and Higher Dose Groups

	Low dose group		*Medium/high dose group*	
Variable	*Mean*	*SD*	*Mean*	*SD*
Voids/day	8.3	2.5	9.6	5.1
Voids/night	0.8	0.8	1.6	1.4
Urgency/day	7.0	2.9	7.9	4.5
Urgency/night	0.7	0.6	1.5	1.0
Leakage/day	2.0	1.3	3.1	2.5
Leakage/night	0.2	0.4	0.8	0.8
FDV (ml)	105.5	68.7	79.6	51.7
MCC (ml)	240.5	148.5	169.3	100.7
Instability index	0.7	0.5	1.2	1.2

In the latter stages of this study a long-term trial of this new compound was instigated and 50% of patients elected to continue medication at the titrated level because of the benefit obtained; 43% of patients had been treated earlier with other medication without a satisfactory response. In none of these patients was any further rise in creatinine noted at 6 months. It is interesting that most withdrawals occurred in the patients who elected to go on to the lowest dose. These patients may tolerate drug side effects as poorly as they tolerate their urinary tract symptoms, which were less severe than in the other treatment groups. This study suggests that emepronium carrageenate is well tolerated and effective and that dose titration is an important factor in obtaining significant benefit. Many patients have tolerated the relatively high doses used in this study without untoward side effects.

Acknowledgements

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The Authors

J. A. Massey, FRCS, Research Fellow, Clinical Investigation Unit, Ham Green Hospital.

P. Abrams, MD, FRCS, Consultant Urologist, Southmead Hospital, Bristol.

Requests for reprints to: J. A. Massey, Clinical Investigation Unit, Ham Green Hospital, Pill, Bristol BS20 0HW.

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Terodiline in the Treatment of Women with Urgency and Motor Urge Incontinence

A Clinical and Urodynamic Double-blind Cross-over Study

T. C. GERSTENBERG, P. KLARSKOV, D. RAMIREZ and T. HALD

Department of Urology, Herlev Hospital, University of Copenhagen, Herlev, Denmark

Summary—In a consecutive double-blind cross-over study, 18 females with detrusor instability were treated with an anticholinergic and calcium antagonistic agent terodiline 25 mg bid or placebo for 3 weeks; cross-over took place after a wash-out period of 1 week. The efficacy of the drug was investigated at the end of each treatment period by means of drug preference, micturition charts, pad usage, bladder and urethral mucosal perception threshold and bulbocavernosus reflex latency measurement. Serum levels of terodiline were estimated at the end of each treatment period and all side effects were reported.

The preference for the drug was statistically significant ($P<0.01$): 14 patients preferred the drug, one preferred the placebo and three had no preference. A small but statistically significant reduction was found in 24-h micturition frequency ($P<0.05$). Cystometry showed an increase in volume at first sensation, an increase in volume at detrusor contraction and a tendency towards an increase in bladder capacity, whereas detrusor contraction pressure was unchanged. Median serum levels of the drug were 559 ng/ml (range 203-1117). No serious side effects were reported.

It was concluded that terodiline should be considered as an alternative drug in the treatment of motor urge incontinence.

Patients with motor urge incontinence have often been a challenge because of the disappointing results of drug treatment. Many different drugs have been used (Andersson and Ulmsten, 1980; Abrams, 1984), including a variety of tertiary and quarternary amines. Parasympaticolytic agents have been preferred in the treatment of motor urge incontinence, but because of poor lipophilic properties, these drugs are inconsistently absorbed from the gastro-intestinal tract. Another group of drugs, calcium antagonists, have been effective both *in vitro* by inhibition of detrusor contraction induced by bladder stimulating drugs on muscle strips (Forman *et al.*, 1978) and *in vivo* in patients with uninhibited detrusor contractions (Rud *et al.*, 1979).

Drugs with combined anticholinergic and calcium antagonistic properties should therefore be effective in the treatment of detrusor overactivity. Terodiline, a drug primarily used as an anti-anginal agent, has shown promising results in women with motor urge incontinence (Ekman *et al.*, 1980; Rud *et al.*, 1980).

Because of the clinical and pharamacological advantages of this drug, a consecutive series of women with motor urge incontinence, in whom previous pharmacological treatment had failed, have been investigated.

Patients and Methods*

Twenty consecutive women with urgency and

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* Methods, definitions and units conform to the standards proposed by the International Continence Society except where specifically noted.

motor urge incontinence were investigated. Their median age was 54 years (range 22-78). The following criteria were fulfilled before entering the study:

(i) Detrusor instability during cystometry in the supine or standing position.
(ii) Maximum flow rate above 15 ml/s.
(iii) Residual urine less than 50 ml.
(iv) Urine culture negative.
(v) Voiding cysto-urethrography in the straight lateral position showing no bladder suspension defect (Olesen and Walter, 1977).

Patients with neurological disease or glaucoma were excluded. All patients had frequency and urgency. Eleven had urge incontinence and used pads and eight claimed to have stress incontinence as well. Six patients had had previous operations for incontinence, 17 had been treated with anticholinergics, mainly emepronium bromide, and 7 with flavoxate. None of these treatments had been effective. Eighteen completed the trial; two patients had to stop the medication in the second period (one on placebo and one on terodiline) because of diseases unrelated to the medication. Informed consent was obtained from all patients.

The trial was designed as a randomised double-blind cross-over study. Patients were allocated at random to terodiline chloride (Bicor, KabiVitrum A/S) 25 mg bid or placebo for 3 weeks, cross-over taking place after a wash-out period of 1 week. All side effects were reported. When attending the clinic at the end of each treatment period, serum samples were taken 2½ h after oral intake of the medication. The following procedure was adopted for testing the effect of the drug.

Micturition charts

A micturition chart over a 3-day period was filled in before and at the end of each medication period. At the end of the trial the patients were asked about drug preference and from the micturition charts the total number of voidings, incontinence episodes and pad usage were selected as parameters of interest.

Urodynamic investigation

The urodynamic investigations, performed before and at the end of each treatment period, consisted of urinary flow measurement, bladder and urethral mucosal perception threshold, bulbocavernosus reflex measurement and CO_2 cystometry with simultaneous EMG recording.

The patients started the examination with a full bladder and a spontaneous flow curve was recorded (Dantec mictiometer). Maximal flow rate (ml/s) and voided volume were calculated or measured.

A Foley catheter with a ring electrode (Dantec, Skovlunde, Denmark) 1 cm below the balloon was inserted transurethrally and the residual urine measured. The ring electrode was used for bladder and urethral perception threshold measurement and external sphincter EMG recording.

Bladder and urethral mucosal perception threshold measurement

The bladder wall perception threshold was measured with the catheter balloon deflated and the ring electrode applied to the bladder wall by means of a slight suction through a side hole in the ring and the catheter. For urethral measurement the balloon was inflated and the catheter withdrawn to the bladder neck. Square wave impulses of 0.2 ms at a rate of 2 Hz were applied with increasing current to the bladder wall and the proximal urethra. The perception threshold was defined as the lowest current able to produce a sensation, *i.e.* when the patient registered a feeling of burning or tingling. At least three recordings were made to ensure consistency and the mean value of the recordings was taken to be the perception threshold.

Bulbocavernosus reflex latency measurement

Single supramaximal square wave stimuli of 0.2 ms were applied to the bladder wall and the posterior urethra through the ring electrode. The reflex response was recorded via bipolar needle electrodes from the anal sphincter, amplified, stored and plotted on an X-Y recorder. The mean value of at least three recordings was used for estimation of the reflex latency.

Cystometry

Rapid fill gas cystometry (100 ml/min) with simultaneous urethral EMG recording were performed with the patient in the lying and standing position. First sensation to void (ml), bladder capacity (ml), volume at detrusor contraction (ml) and detrusor contraction pressure (cm H_2O) were recorded or calculated. Detrusor contractions exceeding 15 cm of water were regarded as diagnostic for detrusor instability. Simultaneous urethral EMG recording was used to rule out neurological pathology. Two to three recordings were made.

Calculations

Statistical calculations were made using non-parametric statistics. The level of significance was 0.05.

Table Median and Range for Micturition Charts, Cystometry, Urethral and Bladder Mucosal Perception Threshold, Bulbocavernosus Reflex Latency and Serum Concentration of Terodiline at the End of the Placebo and Medication Periods

	Placebo	*Terodiline*	
Micturition Chart			
24 h frequency	8.5 (6-21)	7.5 (4-11)	$P<0.05$
Pad usage	2 (1-7)	0 (0-8)	NS
Cystometry			
Residual urine (ml)	0 (0-50)	0 (0-50)	NS
First sensation (ml)	70 (10-170)	90 (10-220)	$P<0.05$
Bladder capacity (ml)	205 (30-380)	240 (40-500)	$0.05<P<0.10$
Volume at detrusor contraction (ml)	90 (10-180)	110 (20-280)	$P<0.01$
Detrusor contraction pressure (cm H_2O)	55 (20-80)	45 (10-80)	NS
Perception Threshold			
Bladder (mA)	23 (17-31)	24 (15-34)	NS
Urethra (mA)	10 (6-19)	10 (4-20)	NS
Bulbocavernosus Reflex Latency			
Bladder (ms)	65 (59-81)	65 (52-85)	NS
Urethra (ms)	68 (49-81)	65 (50-79)	NS
Serum Level (ng/ml)	<5	559 (203-1117)	

NS = No statistically significant difference

Results

Data obtained after placebo treatment were not significantly different from pre-treatment values.

Fourteen of 18 patients (78%, 95% confidence limits 52-94%) reported beneficial effect from terodiline, one patient (6%, 95% confidence limits 0-27%) preferred the placebo and three (17%, 95% confidence limits 4-41%) had no preference. The preference for the drug was statistically significant (sign test, $P<0.01$).

The number of voiding events and pad usage during the last 3 days of the placebo and medication periods are given in the Table and Figure 1. A small but statistically significant reduction in 24-h frequency from a median of 8.5 (range 6-21) to 7.5 (range 4-11) was found in the medication period (Wilcoxon paired test, $P<0.05$).

Eleven patients on placebo had urge incontinence and used pads. During terodiline treatment six patients became continent but no statistically significant difference was found in the number of pads used (Wilcoxon paired test, $P>0.10$).

Cystometric investigations are shown in the Table and Figure 2. First sensation and volume at detrusor contraction had a statistically significant median increase of 29 and 22% respectively and bladder capacity had a tendency towards an increase (Wilcoxon paired test, $P<0.05$, $P<0.01$ and $0.5<P<0.10$ respectively). No significant changes

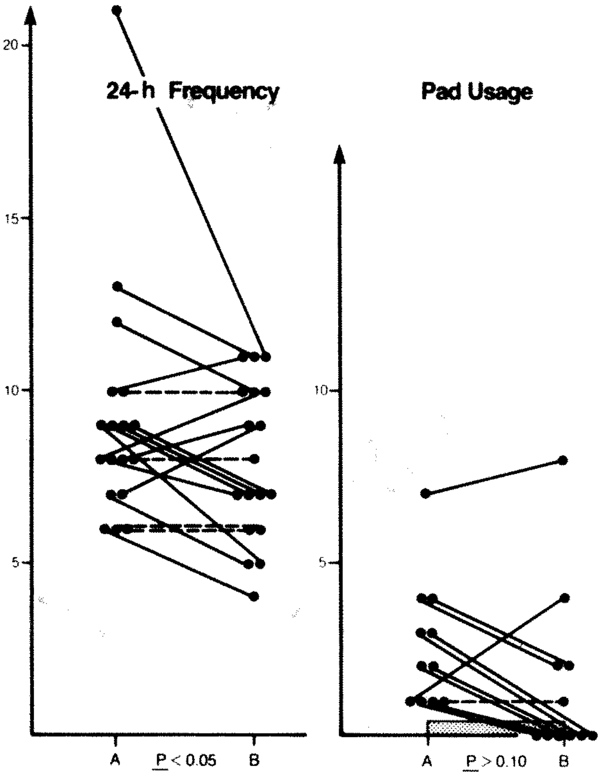

Fig. 1 Micturition charts in 18 women with motor urge incontinence during the last 3 days of the placebo period (A) and medication period (B). The bar represents seven patients.

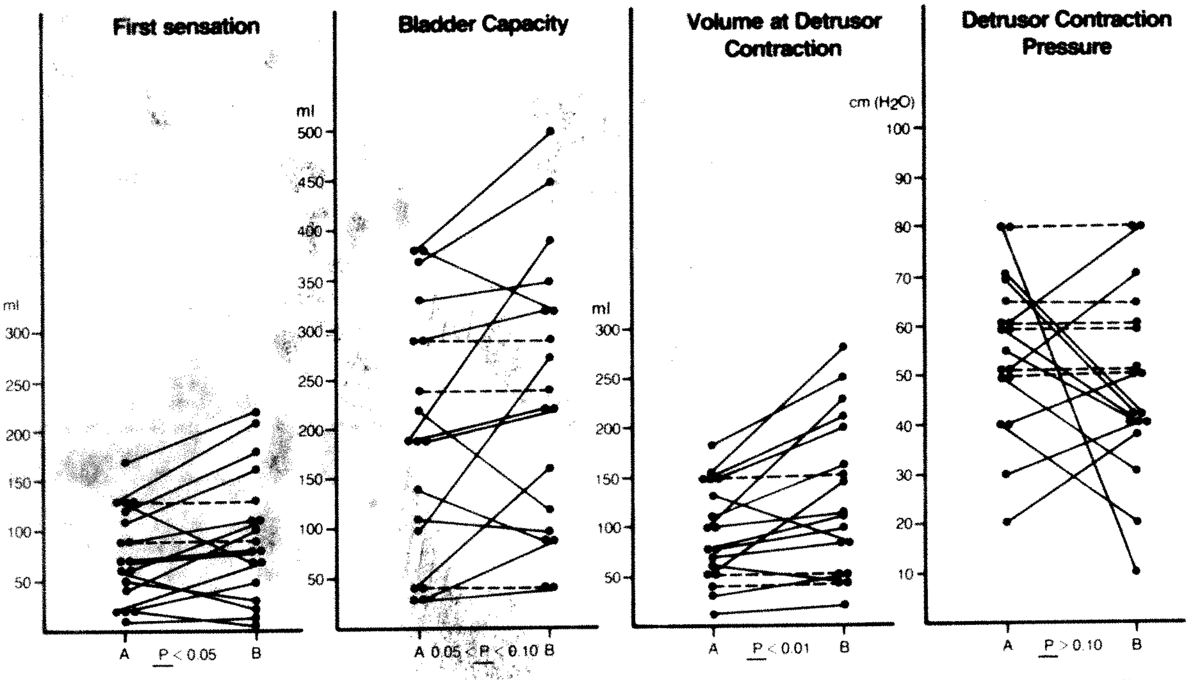

Fig. 2 Cystometric investigation in 18 women with motor urge incontinence during the placebo period (A) and medication period (B).

were found in detrusor contraction pressure or residual urine. Two patients had detrusor instability in the standing position, whereas all of the others had instability in the lying and standing position. All patients had sterile urine.

Bladder and urethral mucosal perception threshold, bulbocavernosus reflex latency and serum levels of the medication are shown in the Table. No significant changes were found in perception threshold and reflex latency, the values being within normal limits. Serum levels of the drug were not statistically significant correlated to the change in micturition frequency, the change in volume at first sensation and the change in volume at detrusor contraction (correlation coefficient Rho 0.25, 0.12 and 0.06 respectively, Spearman rank sum test). No serial side effects were reported. Three patients complained of dryness of the mouth and one of them also had dizziness. Serum levels of the drug were 704, 767 and 1117 ng/ml. All patients continued with the treatment.

Discussion

The beneficial effect of terodiline registered in drug preference was not supported by an equal improvement in the data used as objective measures for incontinence. A small but statistically significant decrease was found in 24-h frequency and cystometry showed an increase in both first sensation and volume at detrusor contraction. The pad usage was also lower on terodiline than on placebo, but the difference did not reach statistical significance. There are two possible explanations for the lack of correlation between the massive subjective preference for the drug and the small objective improvement in symptoms and urodynamic data. Firstly, it could be that the incontinence pattern was altered by the drug. We have observed that the micturition pattern in the patients using pads showed a tendency for pad usage to decrease and the frequency to increase during terodiline treatment, although this trend did not attain statistical significance. Six of 11 patients using pads during placebo treatment became continent on terodiline. Evidently the drug allowed the patients to reach the toilet and void rather than leak. The second possible explanation for the lack of correlation could be that the parameters commonly used to measure incontinence were inappropriate or that they were not used in a proper combination with proper weighting. The voiding volumes were not registered by all of the patients, but it seems from the data that the voided volumes increased during the active medication. The distinct and consistent assessment in favour for the drug, regardless of treatment sequences, was also reported by Peters *et al.* (1984). This finding was ascribed to the subjective assessment being more sensitive than "snapshot" estimates of micturition variables and cystometry.

In accordance with Rud *et al.* (1980), who used only 12.5 mg tid, bladder volume at urgency and volume at detrusor contraction increased, but in contrast to Rud *et al.* (1980), we found no effect on bladder capacity and detrusor contraction pressure. The exact mechanism of neurotransmission responsible for mediating human detrusor activation has not been established. Acetylcholine is not the only transmitter in action (Hindmarsh *et al.*, 1977). The pharmacological effect of terodiline is mainly anticholinergic but in higher doses it also possesses a calcium antagonistic effect (Husted *et al.*, 1980: Østergaard *et al.*, 1980).

Serum levels of the drug necessary to obtain a clinical effect have not been established, but a serum concentration of 350 ng/ml should be effective (Andersson, 1984). In the present study much higher serum levels of the drug have been measured without serious side effects.

No change was found in the bladder and urethral mucosal perception threshold and in the bulbocavernosus latency measurement, which implies that an obvious effect on exteroception or a ganglion blocking effect was not evident.

In conclusion, terodiline appears to be an alternative drug in the treatment of motor urge incontinence. Further studies are needed to establish the effect of the drug, with special emphasis on separating patients with frequency and urinary incontinence and the use of a more reliable incontinence quantification.

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The Authors

T. C. Gerstenberg, MD, Senior Registrar.
P. Klarskov, MD, Senior Registrar.
D. Ramirez, MD, Research Fellow.
T. Hald, MD, PhD, Consultant.

Requests for reprints to: T. C. Gerstenberg, 2 Laurids Bings Alle, DK-2000 Copenhagen F, Denmark.

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Cystometry: Unstable Bladder and Urinary Tract Infection

N. N. BHATIA and A. BERGMAN

Division of Gynecologic Urology, Department of Obstetrics and Gynecology, Harbor/UCLA Medical Center and Cedars-Sinai Medical Center, Los Angeles, USA

Summary—In order to study the effect of urinary infections upon the incidence of bladder instability during cystometric evaluation, 15 women underwent cystometry during the course of significant bacteriuria (10^5 organisms/ml) and again 2 weeks after treatment. The pre-treatment incidence of bladder instability (53%) dropped by 50% following treatment of the infection but other cystometric measurements remained unchanged. Urinary tract infections must be treated adequately before treating bladder instability.

Cystometry is used at an increasing rate in the investigation of patients with lower urinary tract symptoms. The classic symptoms of urinary tract infection (urgency, frequency and nocturia) are similar to those in patients with bladder instability (Cardozo and Stanton, 1980; Stamey, 1980). There is a high incidence of urinary infection in women (Kass *et al.*, 1964; Freedman *et al.*, 1965; Kunin and McCormack, 1968) and the incidence of bladder instability is considerably higher if cystometric evaluation is performed while the urine is infected (Rees, 1978). Recently, routine culturing of urine specimens revealed significant bacteriuria in 7.3% of women undergoing urodynamic studies who were previously found to be free of urinary infection (Bergman and McCarthy, 1983).

The present study was undertaken to determine the accuracy, reliability and reproducibility of cystometry during and after the treatment of urinary tract infection.

Patients and Methods

The demonstration of a negative culture in a catheter specimen of urine is regarded as a prerequisite for all patients referred to the Division of Gynecologic Urology. During a 9-month period in 1983/1984, 183 woman were referred with lower urinary tract problems. Eighteen were found to have significant bacteriuria ($\geqslant 10^5$ organisms/ml). Fifteen of these 18 patients agreed to return for repeat cystometric studies and were included in this study. Nine were pre-menopausal (mean age 42 years), six were post-menopausal (mean age 55 years) and the mean parity was two (range 0-5). During the same period 7 of 15 patients, who were comparable with the study group in age, menopausal status and parity and who had a urodynamic diagnosis of bladder instability, agreed to have cystometric studies repeated 2 weeks after the initial evaluation and before the start of treatment. In both groups another catheter specimen of urine was taken for

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Table 1 Comparison of Results of Cystometry in 15 Patients During and After Treatment of Urinary Infection

Total number of patients	*During urinary infection*	*Following treatment*
	Results changed (6 patients)	
5	Unstable bladder	Stable bladder
1	Stable bladder	Unstable bladder
	Results unchanged (9 patients)	
3	Unstable bladder	Unstable bladder
6	Stable bladder	Stable bladder

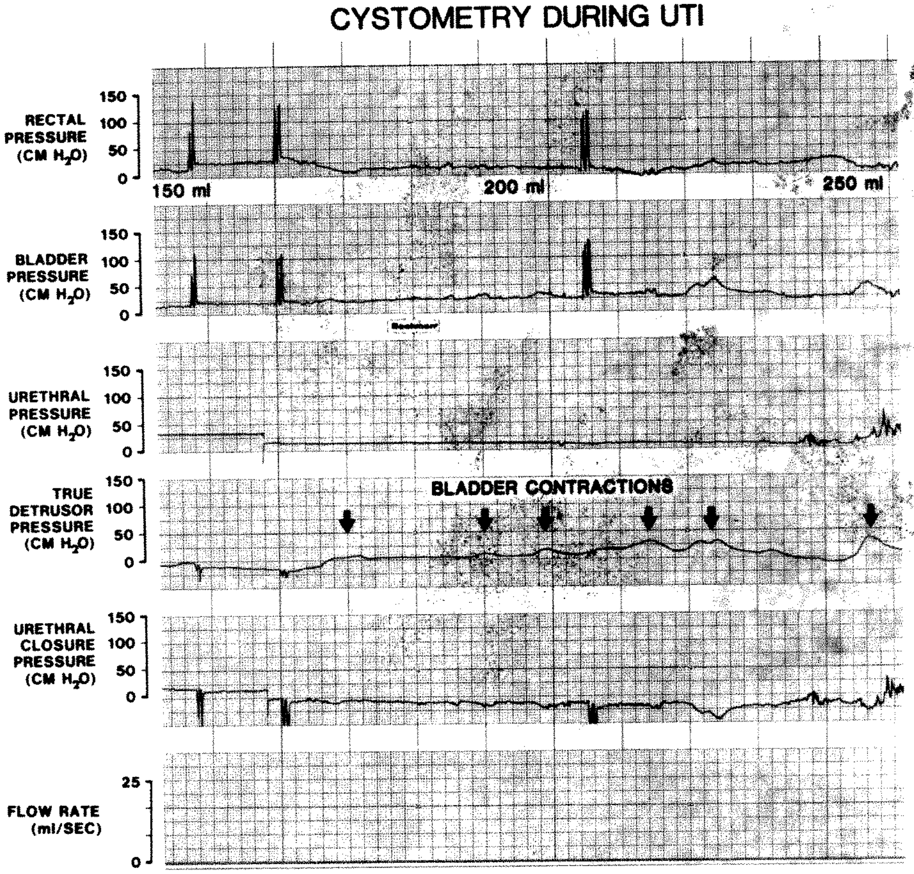

Fig. 1 Simultaneous urethrocystometry during urinary infection. Arrows point to uninhibited detrusor contractions.

culture just before cystometric studies in order to reconfirm the presence of significant bacteriuria.

Cystometry was performed in both study and control groups in the supine and standing position. The bladder was filled transurethrally with normal saline at a constant rate of 60 ml/min and stressful manoeuvres (*e.g.* coughing, heel bouncing and climbing stairs) were used to reveal detrusor instability. The pressure changes in bladder, urethra and rectum were recorded simultaneously using pressure-sensitive microtip transducer catheters (Millar Instruments Inc., Houston, Texas). One catheter (size 8F, Model PC-380) recorded intrarectal pressure and a second catheter (size 7F, Model PC-771) with two microtransducers recorded intravesical and intra-urethral pressures. The true detrusor pressure and urethral closure pressures were obtained by electronic subtraction and were recorded with an eight-channel recorder (Beckman Instruments Inc., Schillar Park, Illinois).

After initial cystometric evaluation all patients in the study group were treated with antibiotics appropriate to the urine culture and sensitivity reports.

Catheter specimens of urine were obtained 2 weeks after treatment and the cystometric studies were repeated.

All terminology conforms to that proposed by the International Continence Society (Bates *et al.*, 1981). Statistical analysis of the results was performed with Student's *t* test for paired data.

Results

Eight of the 15 patients in the study group demonstrated instability when cystometry was performed during the course of urinary infection. After appropriate treatment of urinary infection, five regained bladder stability and showed no uninhibited detrusor contractions at repeat cystometry 2 weeks later (Table 1, Figs 1 and 2). The symptoms of nocturia and urinary frequency continued unchanged in three of the five patients despite restoration of bladder stability. In nine patients the stable or un-

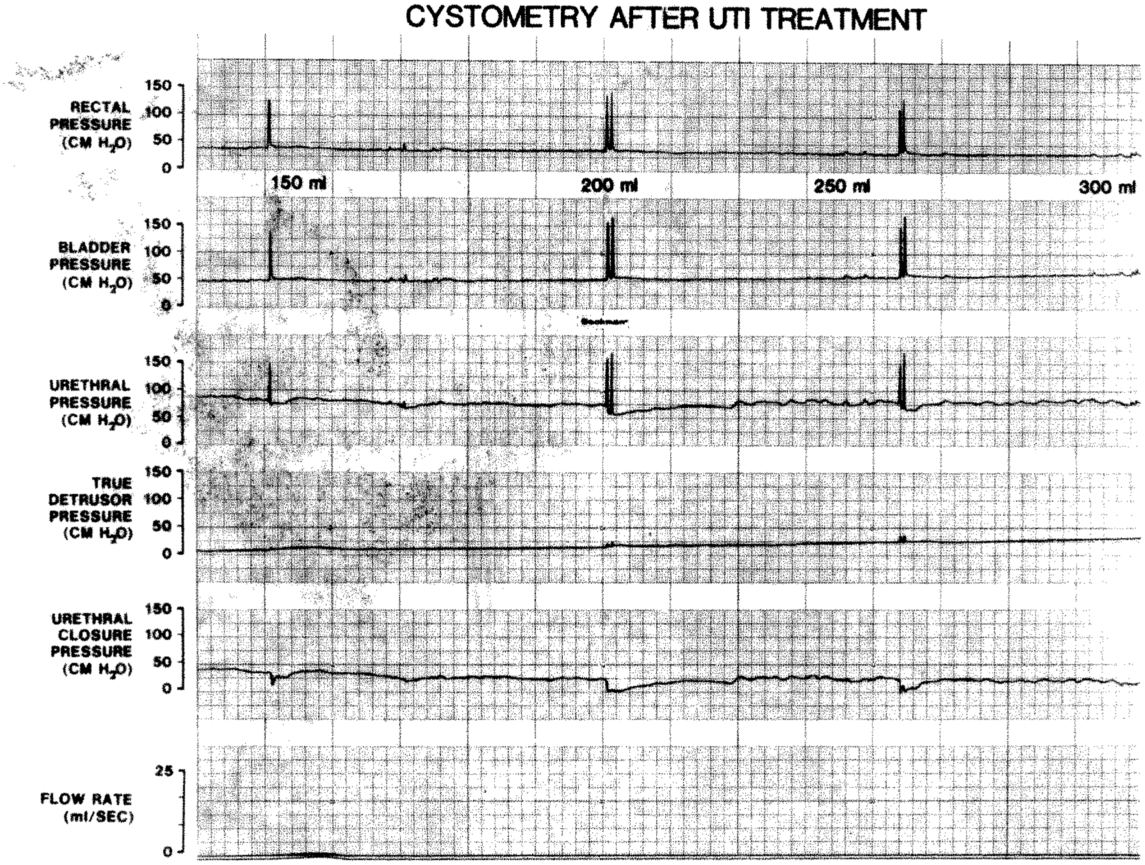

Fig. 2 Cystometry following treatment of urinary infection in the same patient. Note absence of uninhibited detrusor contractions.

Table 2 Cystometry Before and After Treatment of Urinary Infection

	Study group (N = 15)		*Control group (N = 7)*	
Bladder volume (ml)	*During UTI*	*Following treatment*	*Initial evaluation*	*Repeat evaluation*
First sensation mean + SD	60 + 33.7	$74 + 38.6^{NS}$	67 + 31	$69 + 27^{NS}$
Full sensation mean + SD	309 + 100	$326 + 113^{NS}$	317 ± 105	306 ± 112^{NS}
Maximal capacity mean + SD	418 + 149	423 ± 150^{NS}	429 ± 141	412 ± 170^{NS}
Pressure increase mean + SD	12 ± 9	11 ± 13^{NS}	11 ± 9	12 ± 7^{NS}

NS = no statistical significant difference, by paired *t* test
SD = standard deviation
UTI = urinary tract infection

stable state of the bladder did not change after treating the urinary infection (Table 1), although two patients with persistent bladder instability reported a mild improvement in symptoms of urgency and frequency after treatment.

All seven patients in the control group continued to show evidence of unstable bladders when cystometric studies were repeated 2 weeks after the initial evaluation and urinary complaints were unchanged.

Table 2 demonstrates that the various cystometric parameters of bladder sensation and bladder capacity were minimally changed following treatment of urinary infection, but none of the changes was statistically significant. Similar results were observed in the control group.

Discussion

The occurrence of uninhibited detrusor contractions during cystometry provides objective evidence of unstable bladder activity in patients with frequency, urgency and urge incontinence. Although urgency and nocturia are reliable indicators of detrusor instability, 18% of the patients had stable bladders during cystometric evaluation (Awad and McGinnis, 1983). The treatment of bladder instability may be life-long and it is imperative to distinguish true bladder instability from the instability secondary to urinary infection.

Bergman and McCarthy (1983) reported that 7.3% of patients undergoing urodynamic studies for various lower urinary tract symptoms were found to have significant bacteriuria ($\geqslant 10^5$ organisms/ml) immediately before urodynamic evaluation. Cystometry performed when there is significant lower urinary tract infection is unreliable. More than 40% of cystometric examinations performed when the urine was infected were found to be unreliable and the diagnosis had to be revised after the infection had been treated and cystometry repeated.

Some studies have shown that *Escherichia coli* endotoxin has an alpha receptor blocking effect and reduces urethral closure pressure (Nergadh *et al.*, 1977; Raz and Bradley, 1979), and urethral instability has been shown to precede detrusor contractions (Awad and McGinnis, 1983; Hindmarsh *et al.*, 1983). In the present series no significant changes were demonstrated in urethral closure pressure during or after treatment of urinary infection and none of the patients tested at the time of urinary infection showed a drop in urethral closure pressure before a detrusor contraction. It has been postulated by Tanagho *et al.* (1971) that the muscle fibres respond by spasm to any neighbouring irritative focus such as infection, and this leads to irritability, increased reflex activity of the detrusor muscle and spasm of the urethral sphincter.

Our results clearly show that urine cultures should be obtained on all patients before undertaking cystometric evaluation.

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The Authors

N. N. Bhatia, MD, FACOG, Assistant Professor and Director, Division of Gynecologic Urology, Harbor/UCLA Medical Center and Cedars-Sinai Medical Center.

A. Bergman, MD, Clinical Research Fellow, Division of Gynecologic Urology, Harbor/UCLA Medical Center.

Requests for reprints to: N. N. Bhatia, Division of Gynecologic Urology, Harbor/UCLA Medical Center, 1000 West Carson Street, Box 3, Torrance, California 90509, USA.

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Long-term Follow-up of Detrusor Instability Following the Colposuspension Operation

SHIRLEY A. STEEL, C. COX and S. L. STANTON

Departments of Obstetrics and Gynaecology, St George's Hospital, London, and Newcross Hospital, Wolverhampton

Summary—Pre- and post-operative clinical and urodynamic data have been reviewed in 24 women with detrusor instability following colposuspension. Follow-up ranged from 3 to 5 years. Ten women remained asymptomatic throughout; of the remainder, four (28.6%) were improved by drug therapy. With one exception, patients who were symptomatic at the outset remained so at late follow-up.

Detrusor instability is a known complication of some forms of suprapubic surgery to control urethral sphincter incompetence (genuine stress incontinence) (Hald *et al.*, 1975; Cardozo *et al.*, 1979; Jarvis, 1981). Its precise aetiology and natural history are unknown.

The following terms have been defined according to the standardisation of terminology of lower urinary tract function produced by the International Continence Society (1976).

Genuine Stress Incontinence is a clinical condition which is proven urodynamically and is the involuntary loss of urine when the intravesical pressure exceeds the maximum urethral pressure due to an elevation of intra-abdominal pressure and in the absence of a detrusor contraction.

Urgency is a strong desire to void accompanied by a fear of leakage.

Urge Incontinence is the involuntary loss of urine associated with urgency. For the purposes of this study, frequency has been defined as the passage of urine seven or more times during the day and twice or more at night. The International Continence Society (1976) definition of detrusor instability took 15 cm water as the upper limit of normality of detrusor pressure on filling or standing. Cardozo *et al.* (1979) suggested subdivisions according to whether (1) detrusor contractions greater than 15 cm water occurred during the filling phase of cystometry (Group 2a), (2) the pressure exceeded 15 cm water on standing without detrusor contractions (Group 2b), or (3) the pressure exceeded 15 cm water on filling without detrusor contractions (Group 2c). The latter is known as low compliance. In 1979, Cardozo *et al.* described 17 patients who developed detrusor instability following colposuspension performed between 1973 and 1978: on review of their traces, one patient was found to have had detrusor instability pre-operatively. In addition, all patients who underwent colposuspension during 1979 have been reviewed and a further nine patients who developed detrusor instability post-operatively were discovered. This study reviews the clinical and urodynamic data on 25 patients followed up for up to 5 years.

Patients and Methods

Between 1973 and 1979, 148 patients who were referred to the urodynamic clinic with a primary complaint of stress incontinence subsequently underwent colposuspension. At the initial visit a full history was taken and neurological, gynaecological and urological examinations were performed. Pre-operative assessment included examination of

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Table 1 Group 1 Patients Remained Stable; Group 2 Patients Became Unstable

	Group 1 (123)			*Group 2 (25)*		
	Mean	*Range*	*Standard Deviation*	*Mean*	*Range*	*Standard Deviation*
Age (years)	49.2	(28-77)	11.2	50.5	(27-81)	16.5
Parity	2.5	(0-7)	1.7	2.3	(0-6)	1.3
Previous operations for incontinence	0.59	(0-4)	0.7	1.1	(0-3)	1.0

Table 2 Mean Age and Parity and Mean Number of Previous Bladder Neck Operations of Patients in Group 2, Distinguishing Between Symptomatic and Asymptomatic patients

	Group 2					
	Symptomatic (14)			*Asymptomatic (11)*		
	Mean	*Range*	*Standard Deviation*	*Mean*	*Range*	*Standard Deviation*
Age (years)	49.6	(27-81)	15.1	54.4	(41-74)	12.7
Parity	2.7	(1-6)	1.3	1.8	(1-3)	0.9
Previous operations for incontinence	0.86	(0-3)	0.86	1.1	(0-3)	1.22

a mid-stream specimen of urine, measurement of peak flow rates and synchronous pressure-flow recordings during bladder filling and voiding by cystometry or videocystourethrography (VCU) (Bates *et al.*, 1970). If stress incontinence was not demonstrable on physical examination or at cystometry, a Urilos or perineal pad test was performed (Stanton and Ritchie, 1977). A diagnosis of urethral sphincter incompetence was made if there was objective evidence of stress incontinence in the absence of detrusor instability. These patients were treated surgically with a modified colposuspension (Burch, 1961; Stanton *et al.*, 1976), preceded by cystoscopy.

Post-operatively, patients were reviewed clinically at 2 to 3 months and either cystometry or VCU was performed at 3 to 6 months on all except six patients who failed to attend. Thereafter patients attended for yearly follow-up. On the basis of initial post-operative urodynamic assessment, patients were classified as having stable detrusors (Group 1—123 patients) or unstable detrusors (Group 2—25 patients). Of the latter, two patients were followed up at 3 years, three patients at 4 years and 20 patients at 5 years or more. At late follow-up, urodynamic assessment was performed on all patients who were symptomatic except in five cases for the following reasons: patient refusal (1), patient lost to follow-up (1), residence too far from the unit for recall (2) and patient too old to justify recall (1).

Results

At the first post-operative urodynamic assessment, 123 patients (80.9%) had stable detrusors and 25 (16.6%) had unstable detrusors. The mean ages, parities and number of previous operations for incontinence are shown in Tables 1 and 2. There was a greater incidence of previous bladder neck surgery in Group 2 but this was not statistically significant. However, with an increasing number of previous bladder neck operations there was a significant trend towards the development of detrusor instability post-operatively. There was no significant difference in the pre-operative symptomatology between the two groups. After surgery there was a significant improvement in all symptoms in Group 1 ($P<0.005$, Man-Whitney test) but no statistically significant improvement in nocturnal frequency, urgency and urge incontinence in Group 2, which is to be expected (Table 3). When comparing the post-operative symptomatology of the two groups, those in Group 2 were more likely to continue to complain of nocturia, urge and stress incontinence and there was a significantly greater proportion of patients in Group 2 (56%) who had objective evidence of stress incontinence due to detrusor instability at 2 to 3 months compared with those in Group 1 (16.2%) (Table 4). There was no significant difference in parameters measured by urodynamic assessment between the two groups, either pre- or post-operatively, apart from the

Table 3 Comparison of Symptoms and Signs in Groups 1 and 2 Shown as Percentages of Patients. Late Follow-up was at 3-5 years

	Group 1 (123)		*Group 2 (25)*		
	Pre-op.	*Post-op.*	*Pre-op.*	*Post-op.*	*Late F.U.*
Frequency:					
diurnal	61.8	37.4*	64.0	36.0*	32.0
nocturnal	32.5	15.5*	40.0	40.0	40.0
Urgency	63.4	30.9*	64.0	36.0	40.0
Urge incontinence	52.0	17.1*	60.0	36.0	32.0
Stress incontinence	100.0	6.5*	100.0	16.0*	12.0
Cystocele	50.4	2.4	56.0	4.0	0.0

* $P<0.005$

Table 4 Comparison of Urodynamic Data between Groups 1 and 2

	Group 1				*Group 2*			
	Pre-op.		*Post-op.*		*Pre-op.*		*Post-op.*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Residual (ml)	5.4	17.6	46.7	79.4	8.3	21.6	29.8	37.0
PR1 (cm H_2O) (Pressure rise on filling)	4.4	3.7	5.4	3.8	5.4	3.8	17.2	9.2
PR2 (cm H_2O) (Pressure rise on standing)	2.3	3.45	3.2	3.7	2.8	3.3	10.0	11.0
Maximum voiding pressure (cm H_2O)	29.9	16.0	41.5	18.9	27.5	12.7	36.0	16.1
Peak flow rate (ml/s)	22.0	9.4	16.9	8.9	21.2	9.1	14.2	7.4
Stress incontinence (%)	100		16.2		100		55	

expected differences in the pressure rise on filling (PR 1) and on standing (PR 2) (Table 4). The urodynamic assessment of patients at late follow-up was not included in this analysis as the numbers were too small for statistical analysis. The incidence of pre- and post-menopausal women in each group was similar. There did not appear to be a relationship between the post-operative finding of a reduced peak flow rate and the development of detrusor instability.

Table 2 compares the ages, parity and previous surgical history of patients in Group 2. There was no statistically significant difference in these characteristics between the two sub-groups.

In five of eight patients on whom urodynamic data were available at late follow-up, the type of detrusor instability remained unchanged (Table 5). In one patient, the type changed from 2a to 2b; one patient, originally asymptomatic, became symptomatic but stable. With one exception, at follow-up all who were symptomatic remained so.

The response to medical treatment was poor (Tables 6 and 7); only four of 14 symptomatic patients were helped by drugs.

Discussion

Detrusor instability is not necessarily associated with the presence of symptoms and in this study the proportion of patients with symptoms varied according to the type of instability (Table 5).

Pre-operative features which militate against a successful outcome after incontinence surgery include increased age, previous incontinence surgery and the presence of detrusor instability (Arnold *et al.*, 1973; Stanton *et al.*, 1978). Although all patients included in this study had stable detrusor function pre-operatively, it was found that with an increase in the number of previous bladder neck operations, the development of post-operative detrusor instability was more likely. There are several reports of the development of detrusor instability following bladder neck surgery (Hald *et al.*, 1975; Jarvis, 1981). It appears that repeated dis-

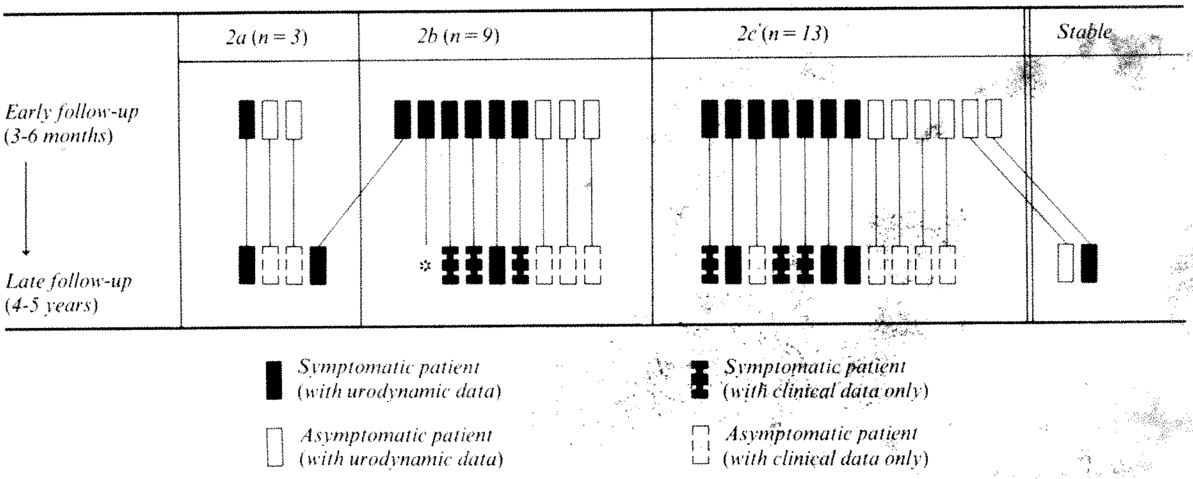

Table 5 Summary of Natural History of Detrusor Instability Following Colposuspension in 25 Patients

2a (n = 3)
2b (n = 9)
2c (n = 13)
Stable
Early follow-up (3-6 months)
Late follow-up (4-5 years)
Symptomatic patient (with urodynamic data)
Symptomatic patient (with clinical data only)
Asymptomatic patient (with urodynamic data)
Asymptomatic patient (with clinical data only)

Table 6 Medical Treatment of Detrusor Instability Following Colposuspension

	Group 2		
Number of symptomatic patients	*2a* *1/3*	*2b* *6/9*	*2c* *7/13*
Patients improved without drugs	0	0	1
Patients improved with drugs	0	0	4
Patients with no improvement after drugs	1	4	2

Table 7

Drug	*Dosage*
Bromocriptine	2.5 mg bd
DDAVP	20 μg *nocte*
Emepronium bromide	200-400 mg tds—qds
Flavoxate hydrochloride	200-400 mg tds—qds
Indomethacin	50 mg tds
Imipramine hydrochloride	25-50 mg tds
Oxybutinin hydrochloride	5-10 mg tds—qds
Propantheline	15-60 mg qds

section in the region of the bladder neck in some way results in a compromised detrusor muscle, perhaps by interference with the nerve supply as postulated by Cardozo *et al.* (1979).

The mean age and parity of Groups 1 and 2 was almost identical. Whether or not a patient with instability would develop symptoms did not seem to be related to the number of previous bladder neck operations. Patients in Group 2 were also less likely to achieve cure of their stress and urge incontinence than those in Group 1.

Drugs used in the treatment of detrusor instability in this study are listed in Table 7. They were used in a random manner and for periods of at least 1 month, or longer if the patient reported an improvement. Some drugs such as bromocriptine were used as part of a drug trial for short periods only.

Anticholinergic preparations and beta-adrenergic stimulants are reported to help 50 to 80% of patients with detrusor instability (Stanton, 1973) but in this study only 16% of patients noticed any improvement.

Cystoscopy is not a mandatory investigation. It was used in this context because many patients had had previous bladder neck surgery, where there was always the risk of finding an unabsorbed suture in the bladder which should be detected before further surgery. In addition, many patients complained of urgency and frequency and it is relevant to exclude any intravesical pathology which may cause these symptoms. No abnormalities were found in this series.

In conclusion, detrusor instability occurred in 24 patients (16%) after colposuspension for urethral sphincter incompetence. Ten women remained asymptomatic. Those patients who were symptomatic at the outset appeared to remain so at late follow-up. Most patients on whom urodynamic data were available 4 to 5 years post-operatively remained unstable.

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The Authors

Shirley A. Steel, MRCOG, Registrar, Department of Obstetrics and Gynaecology, St George's Hospital, London.

C. Cox, MRCOG, Consultant Obstetrician and Gynaecologist, Newcross Hospital, Wolverhampton.

S. L. Stanton, FRCS, FRCSE, MRCOG, Consultant Gynaecologist, St George's and St James' Hospitals, London.

Requests for reprints to: Shirley A. Steel, Department of Obstetrics and Gynaecology, St George's Hospital Medical School, Lanesborough Wing, Cranmer Terrace, London SW17 0RE.

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Trophoblastic Metaplasia in Urothelial Carcinoma of the Bladder

A. F. BURRY, S. R. MUNN, E. P. ARNOLD and C. U. McRAE

Departments of Urology, Surgery and Anatomical Pathology, Christchurch Hospital, Christchurch, New Zealand

Summary—Trophoblastic differentiation in bladder carcinoma is reported in four patients. Plasma gonadotrophin (beta subunit of HCG), measured in three patients, was elevated. In one patient treated with cisplatin, vinblastine and bleomycin, the β HCG level fell significantly but progression of malignant disease was not arrested.

Pure extragonadal chorionepithelioma is rare but has been reported not only in mediastinum, retroperitoneum and pineal but also in liver and stomach (Fine *et al.*, 1962). Trophoblastic differentiation (metaplasia) in other types of tumour appears more common and has been reported in such organs as liver (Floyd and Cohn, 1973), lung (Beck *et al.*, 1970) and bone (Kalra *et al.*, 1984). Occasional cases have been reported as chorionepithelioma in the bladder (Weinberg, 1939; Hyman and Leiter, 1943; Ainsworth and Gresham, 1960). Some trophoblastic tumours of the bladder have evolved from transitional cell carcinoma (Civantos and Rwylin, 1972; Kawamura *et al.*, 1978; Obe *et al.*, 1983). Recently, using immunoperoxidase staining, Dennis and Turner (1984) demonstrated HCG-secreting trophoblastic elements in a case of transitional cell carcinoma of the bladder.

We report four recent cases of bladder carcinoma with trophoblastic metaplasia confirmed by immunoperoxidase staining for β HCG.

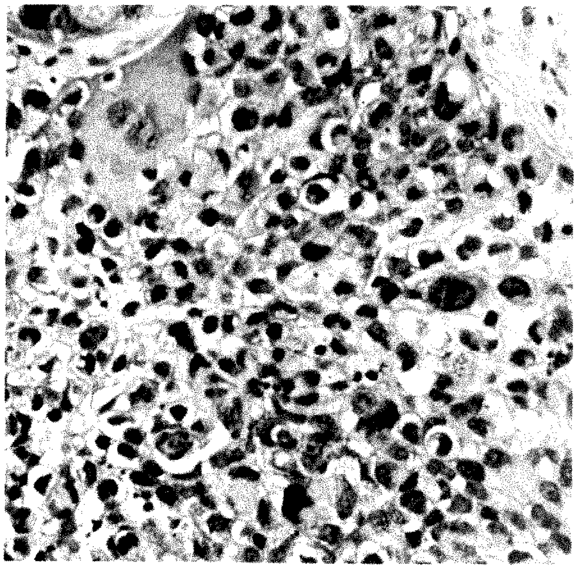

Fig. 1 Case 2. First tumour. Poorly differentiated transitional cell carcinoma with multinucleated giant cells. No lymphocytic response. (H and E × 175).

Patients and Methods

Two cases were identified in the course of histological examination of biopsy material, a third from biopsy of an enlarged lymph node and the fourth as a result of incidental finding of a raised urinary HCG level. All histological material available for each patient was reviewed by AFB. Histological diagnosis of trophoblastic differentiation was based on the presence of multinucleated giant cells with acidophilic cytoplasm, often applied to the surface of masses of polyhedral cells (Fig. 1). These giant cells had typical appearances of syncytiotrophoblast. Related cells were often large with clear cytoplasm

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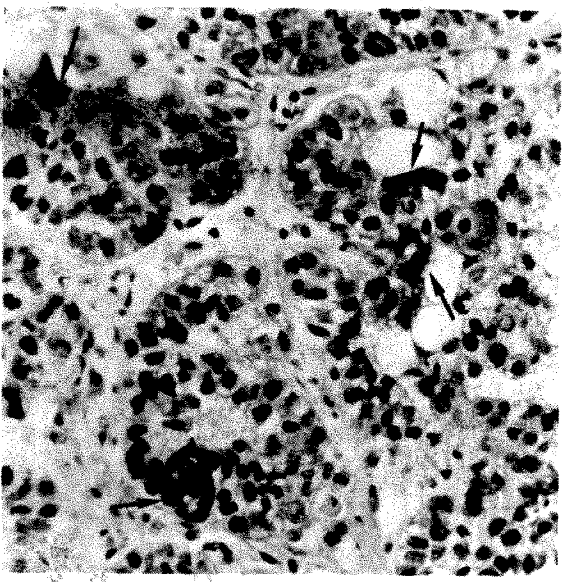

Fig. 2 Case 2. Second tumour. Syncytiotrophoblastic cells stained darkly by immunoperoxidase technique.

(? cytotrophoblast) but merged with cells that were clearly transitional cell carcinoma. HCG staining confirmed multinucleate cells as syncytiotrophoblast (Fig. 2) but also stained some mononuclear cells, although usually less strongly.

Beta HCG was demonstrated in tissue by routine immunoperoxidase techniques using the Hsu ABC technique (Hsu *et al.*, 1981), in a kit supplied by Vector Laboratories, and antiserum to β HCG from Dakopatts A/S. Serum and urinary β HCG were determined by radioimmunoassay based on a kit supplied by Serono Laboratories. The kit has high sensitivity and low cross reactivity with luteinising hormone. In our laboratory normal men and non-pregnant women have serum HCG levels less than 5 iu/ml.

Case 1

A male aged 43 gave a 4-month history of frequency and haematuria and a mass he had discovered in the left iliac fossa. A large fungating mass was found in the bladder; it obliterated the left ureteric orifice and on bimanual examination was found to be fixed to the lateral pelvic wall. After 2400 cGy of radiotherapy, enlarging nodes were found in the right supraclavicular fossa. He sought assistance from alternative medicine and 4 months later the β HCG level was 45. He was given two cycles of chemotherapy with cisplatin, vinblastine and bleomycin, and 2 months later the β HCG had fallen to 5. However, further metastases occurred and these failed to respond. He died 10 months after presentation.

Case 2

A 53-year-old woman presented with painless haematuria due to a 3-cm infiltrating transitional cell carcinoma. Following 500 cGy a partial cystectomy was performed. She remained well for 7 years, when further haematuria led to the discovery of a T2 tumour with pelvic nodal involvement on CT scanning. Local radiotherapy stopped the bleeding but 3 months later pulmonary metastases appeared. At this time the β HCG was greater than 20,000 iu/l. Methotrexate was ineffective and she died 2 months after the second tumour presented.

Case 3

A woman of 56 presented with a short history of haematuria and suprapubic pain due to a solitary transitional cell carcinoma of the bladder. Resection was associated with severe haemorrhage. Two months later she was readmitted with severe bleeding and required 11 units of blood. She failed to respond to radiotherapy and died from pulmonary metastases 5 months after presentation.

Case 4

A 66-year-old man developed left loin pain due to a large bladder tumour obstructing the left ureter and fixed to the lateral pelvic wall (T4). The serum β HCG was 460 iu/l. Three months after radiotherapy this had fallen to 110 iu/l and there was local tumour regression, but fixity remained and he died from pulmonary metastases 4 months after presentation.

The pathological findings are summarised in the Table. Syncytial cells varied in number from case to case and there was a rough correlation between numbers present and serum β HCG levels. The proportion of apparent trophoblastic tissue was higher in metastases but in none of our material was pure chorionepithelioma encountered. Lymphocyte infiltration at the interface between infiltrative tumour and host tissue was inconspicuous in three cases.

Discussion

While large quantities of β HCG are secreted in the placenta and in trophoblastic tumours of the testis, small amounts of HCG have been detected in normal human tissues and in a variety of tumours (Yoshimoto *et al.*, 1979). Beta HCG was detected histologically in 25 of 28 tumours by McManus *et*

Table Pathological Findings

Primary tumour	*Grade*	*Giant cells*	*HCG by immunoperoxidase*	β *HCG*	*Lymphocyte response*
1. Large T4	TCC Grade 3	+	+	45 iu	+ - + +
2. (a) T2	Infiltrating transitional cell carcinoma	+ +	+ +	Not determined	+
Seven years later (b) T2	Anaplastic Grade 3 TCC	+	+ +	> 20,000 iu	±
3. T3	Grade 3 TCC	+ +	+ + +	Not determined	±
4. Large T4	Grade 3 TCC	+ +	+ + +	460 fell to 110 iu	±

al. (1976) using immunoperoxidase staining. Increased serum levels of β HCG were noted in 16 of 99 patients with non-malignant disease and in the same proportion of 414 patients with malignant disease (Dosogne-Guériu *et al.*, 1978). However, higher levels were encountered with some of these cancer cases. It appears, therefore, that a significant proportion of malignant tumours are associated with secretion of β HCG, usually at low levels.

In patients with tumours of the bladder and ureter, raised levels of β HCG in blood and/or urine have been reported. Thus Lange *et al.* (1976) found mildly elevated plasma β HCG levels in four of 50 patients with transitional cell carcinoma of the bladder and Fukatani *et al.* (1983) reported raised levels of urinary HCG in two of 10 patients with bladder tumours and in one of two patients with carcinoma of the ureter. Serum HCG levels in these cases were normal or only slightly elevated. These biochemical surveys were not correlated with histological evidence of HCG secretion. However, in cases of bladder carcinoma showing trophoblastic differentiation reported by Civantos and Rwylin (1972) and Kawamura *et al.*, (1978), high levels of gonadotrophin secretion were demonstrated. The exploitation of immunoperoxidase staining techniques has now made it possible to identify HCG-secreting elements in biopsy material (Dennis and Turner, 1984). In our four patients we have used this technique to confirm subjective histological diagnosis of trophoblastic differentiation. The fact that four patients have presented in a relatively small population over a period of 2 years suggests that trophoblastic differentiation in bladder carcinoma, implied by biochemical measurements, may be relatively common and has thus far largely escaped unnoticed. In our small series it appears to be associated with poorly differentiated urothelial carcinoma and carried a poor prognosis in three of the four patients. The fourth survived for 7 years. Fukatani *et al.* (1983) associated raised excretion of urinary β HCG with tumours of poor differentiation or of advanced clinical stage.

Immunoperoxidase staining greatly facilitates the identification of syncytiotrophoblastic cells, which tend to be applied to the surface of sheets of urothelial carcinoma cells. Histological distinction of cytotrophoblast from poorly differentiated large cell transitional cell carcinoma is not possible, but positive immunoperoxidase staining may be considered to imply a trophoblastic differentiation. However, most positively staining elements in our material were clearly syncytial.

Human chorionic gonadotrophin is an inhibitor of the T cell response and it has been suggested that it is a factor in the non-rejection of the placenta (McManus *et al.*, 1976). Although McManus *et al.* demonstrated β HCG secretion on the surface of tumour cells in 25 of 28 malignant human tumours, indicating that secretion of HCG is common, elaboration of *large* amounts of HCG may influence host response and prognosis. Certainly all of our cases were of high grade malignancy. It is notable also that lymphocytic response to tumour in our material was minimal or of low grade in keeping with the diminished host reaction.

In Case 1, treatment specifically directed at trophoblastic tissue failed to influence the course of the disease. Nevertheless, a more extended trial of antitrophoblast therapy in combination with conventional treatment may be warranted in cases of urothelial malignancy with raised plasma or urinary HCG levels.

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The Authors

A. F. Burry, FRCPA, Anatomical Pathologist.
S. R. Munn, MB, ChB, Surgical Registrar.
E. P. Arnold, PhD, FRCS, FRACS, Associate Professor of Urology.
C. U. McRae, FRCS, FRACS, Consultant Urologist.

Requests for reprints to: A. F. Burry, Department of Anatomical Pathology, Christchurch Hospital, Christchurch, New Zealand.

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Treatment of Superficial (T1) Tumours of the Bladder by Radical Radiotherapy

P. M. QUILTY and W. DUNCAN

Department of Clinical Oncology, Western General Hospital, Edinburgh

Summary—Local tumour control and survival is reported for 190 patients with T1 transitional cell cancer of the bladder who received a radical course of X-ray therapy. There was no difference in survival by the histological grade of the cancer but patients with grade 3 cancers had the highest probability of local control. After initial complete local tumour regression there was a similar probability of subsequent distant metastases irrespective of the grade of the cancer.

Radical small field beam directed radiotherapy is commended for patients with T1/pT1 grade 3 transitional cell cancer of the bladder.

There is still debate about the role of radiotherapy in the management of superficial cancers of the bladder. Most superficial tumours (T1/pT1) are normally dealt with by endoscopic resection or cystodiathermy. Intravesical chemotherapy has been increasingly used in patients with multiple tumours which are often difficult to control endoscopically. However, results in T1 cancers have been reported as disappointing (MacFarlane *et al.*, 1985). Radiation therapy has been thought to be less than optimal, even for those patients with tumours at high risk of progression (Whitmore and Prout, 1982). Long-term local control has not been good.

In many studies it has been found that the histological grade of the cancer, the number of tumours present and the tumour size predict the risk of tumour recurrence or progression for endoscopically managed patients with pTa/pT1 cancers (England *et al.*, 1981; Pocock *et al.*, 1982; Dalesio *et al.*, 1983; Smith *et al.*, 1983). Tumour progression has been found to be significantly more common in patients with recurrent T1 cancers (Lutzeyer *et al.*, 1982). In addition, patients with T1 cancer have a significantly poorer survival than those with Ta cancer (Pocock *et al.*, 1982). Their observations suggest that patients with T1 grade 3 cancer should be managed using treatments in addition to endoscopic resection, particularly if the tumour is recurrent after an initial attempt at endoscopic management.

Patients and Methods

This study reviews the results of radical megavoltage X-ray therapy in 190 patients with stage T1 transitional cell carcinoma of the bladder referred to the Department of Clinical Oncology between 1971 and 1982. The radiotherapy service provided by the department covers a large area of south-eastern Scotland. One hundred and two patients (53.7%) were referred by general surgeons in the district general hospitals of the region. Sixty-two (32.6%) were referred for radiotherapy by the urologists at the Western General Hospital in Edinburgh and 26 (13.7%) by the urologists at the Royal Infirmary of Edinburgh during this 12-year period.

The mean age of the patients was 64.4 years (SE 0.75) with a range of 29 to 85 years.

Ninety-eight patients (51.6%) had undergone previous therapy for their bladder cancers, 85 by a transurethral resection (TUR). In 61/85 patients the initial treatment had been given more than 3 months before the commencement of radiotherapy.

The morphology of the tumour at cystoscopy

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Table 1 Distribution by Histological Grade

Histological grade	*Numbers*	*% of total*
Grade 1	93	48.9
Grade 2	36	18.9
Grade 3	37	19.5
Ungraded (GX)	24	12.6
Total	190	

had been recorded precisely in 187 patients. One hundred and thirty-seven (73.3%) had papillary tumours and 19 (10.2%) had solid tumours. The appearance was mixed, papillary/solid in 29 patients (15.5%) and only two had tumours that were reported as being ulcerated. The mean tumour size was 3.9 cm (SE 0.17). In 70% of patients assessed for tumour size, this was less than 5 cm and very few patients had tumours exceeding 7 cm.

The histological grade of the tumour had been assessed in 166 patients (Table 1). Ninety-three patients (48.9%) had well differentiated cancers. Patients with grade 3 cancer comprised only 12.7% of patients referred from district hospitals compared with 27.3% of those referred from urologists in Edinburgh.

No assessment of the number of tumours present was made in five patients. Seventy-five patients had solitary tumours, 55 had multiple tumours and 55 had diffuse involvement of the bladder by tumour.

One third of grade 1 and grade 2 tumours were solitary compared with 52.8% of grade 3 tumours (Table 2). Tumours were solitary in only 38% of patients with papillary cancers compared with 12/20 (60%) when the tumour appeared solid or ulcerated. Papillary tumours were assessed as grade 1 (well differentiated) in 66.9% of cases. When the tumour appeared solid or ulcerated, 94.1% of those assessed were grade 2 or grade 3 cancers. The histological grade of the cancer was significantly correlated with its morphological appearance at cystoscopy ($\chi^2 = 26.6$, df = 4, $P < 0.01$) (Table 3).

Treatment Techniques

Treatments were given by 4, 6 or 9 MV linear accelerators. Most patients were treated by a three-field beam directed technique (one anterior and two posterior oblique fields) using small fields, usually 10.0 cm × 10.0 cm to cover the whole bladder. All patients received a target absorbed dose of at least 50.0 gray. The modal absorbed dose was 50.0 gray, given in 20 fractions over 4 weeks.

Results

Survival rates, local tumour control and metastasis-free rates are reported from the date of commencement of radiotherapy. All deaths, including those certified as being due to intercurrent disease, were included in the actuarial survival analyses. The survival rates were not age-corrected. Patients were reviewed to 31 December 1983 and none was lost to follow-up.

Local tumour regression. Of the 190 patients who completed radical radiotherapy 174 were assessed for tumour response at a follow-up cystoscopy, bimanual examination and, when indicated, biopsy. Eighty-three patients (48%) achieved complete tumour regression and the remaining 91 patients had either residual tumour at the original site or recurrent tumour elsewhere in the bladder.

Local regression was significantly related to the morphological appearance of the cancer; 40.3% of patients with papillary tumours achieved initial complete local regression following radiotherapy compared with 58.3% of those with mixed (papillary/solid) tumours. When the tumour was solid or ulcerated 70% of patients had complete regression ($\chi^2 = 7.6$, df = 2, $P < 0.05$).

Significantly fewer patients with grade 1 cancers achieved complete local regression compared with those with either grade 2 or grade 3 cancer. The histological grade of the cancer was significantly associated with the proportion achieving complete local regression ($\chi^2 = 13.6$, $P < 0.01$) (Table 4).

Table 2 Distribution by Histological Grade and Number of Tumours

Number of tumours	*Histological grade*				
	G1	*G2*	*G3*	*Ungraded*	*Total*
Solitary	30 (33.3%)	12 (33.3%)	19 (52.8%)	14	75
Multiple	29 (32.2%)	14 (38.9%)	8 (22.2%)	4	55
Diffuse	31 (34.4%)	10 (27.8%)	9 (25.0%)	5	55
Total	90	36	36	23	185

Table 3 Distribution by Morphological Appearance and Histological Grade

	Appearance			
Histological grade	*Papillary*	*Mixed*	*Solid/ ulcerated*	*Total*
Grade 1	79	13	1	93
Grade 2	23	5	7	35
Grade 3	16	9	9	34
Ungraded (GX)	15	1	4	20
Total	133	28	21	182

Table 4 Local Tumour Regression by Histological Grade and Number of Tumours

Grade	*Total assessed*	*Complete local regression*	*Local control at 5 years (actuarial % + SE)*
Grade 1	88	29 (33.0%)	16.1% (±4.2)
Grade 2	33	19 (57.6%)	29.3% (±8.5)
Grade 3	31	21 (67.7%)	55.6% (±8.7)
Ungraded (GX)	23	14 —	—
Total	175	83 (47.4%)	27.7% (±3.5)
Number of Tumours			
Solitary	69	37 (53.6%)	35.1% (±5.8)
Multiple	51	20 (39.2%)	22.6% (±6.4)
Diffuse	50	21 (42.0%)	20.5% (±5.9)
Total	170	78	

More patients with solitary tumours had complete regression (53.6%) than those with either multiple (39.2%) or diffuse tumours (42.0%) (Table 4). The difference was not statistically significant.

Overall survival. The actuarial 5-year survival rate of patients who completed a radical course of X-ray therapy was 60.8% (±3.8%) and 33.0% (±5.6%) at 10 years (Fig. 1).

The equality of the survival distribution for patient subgroups was tested using the Mantel-Cox (logrank) test.

Tumour appearance and survival. There were 133 patients with papillary tumours and their actuarial 4-year survival rate was 69.3% (±4.1%). Twenty-eight patients had mixed tumours and their 4-year survival rate was 61.5% (±9.7%). Twenty-one patients had solid or ulcerated tumours; their 4-year survival rate was 65.6% (±10.6%). The difference in survival distributions by tumour appearance was not significant ($P = 0.38$) (Fig. 2).

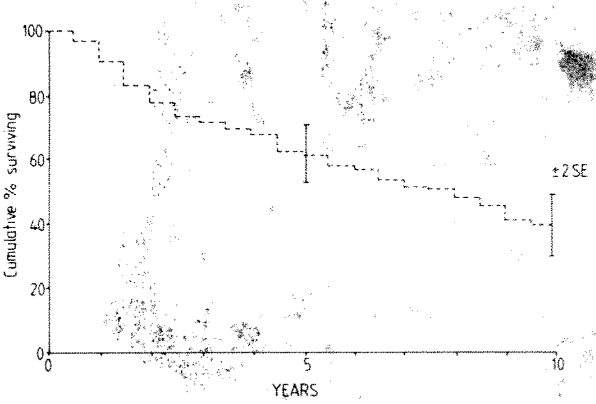

Fig. 1 T1 transitional cell carcinoma. Overall (actuarial) survival for 190 patients who received a radical course of X-ray therapy.

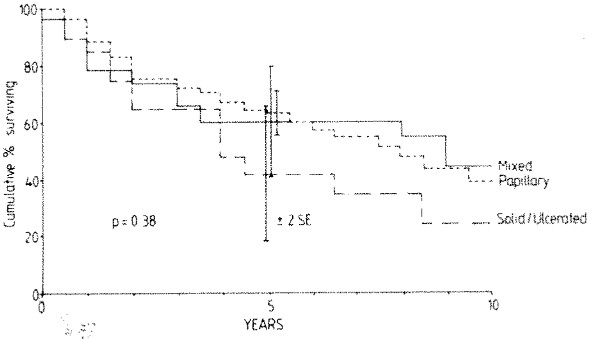

Fig. 2 T1 transitional cell carcinoma. Survival by tumour appearance (Generalised savage (Mantel-Cox) test) ($P = 0.38$).

Histological grade and survival. The 5-year survival rate for patients with grade 1 T1 cancer was 64.5% (±5.1%) compared with 53.5% (±9.5%) for those with grade 3 T1 cancer. There was no significant difference in survival distribution by histological grade ($P = 0.49$) (Table 5).

Local tumour regression and survival. Complete tumour regression at the first follow-up cystoscopy was not correlated with the probability of long-term survival. The actuarial 5-year survival rate

Table 5 Survival Rate by Histological Grade

		Actuarial (%) Survival Rate (± SE)	
Grade	*Nos.*	*5 years*	*10 years*
Grade 1	93	64.5% (±5.1)	41.4% (±7.8)
Grade 2	36	62.6% (±8.8)	18.0% (±14.6)
Grade 3	37	53.5% (±9.5)	30.8% (±10.9)

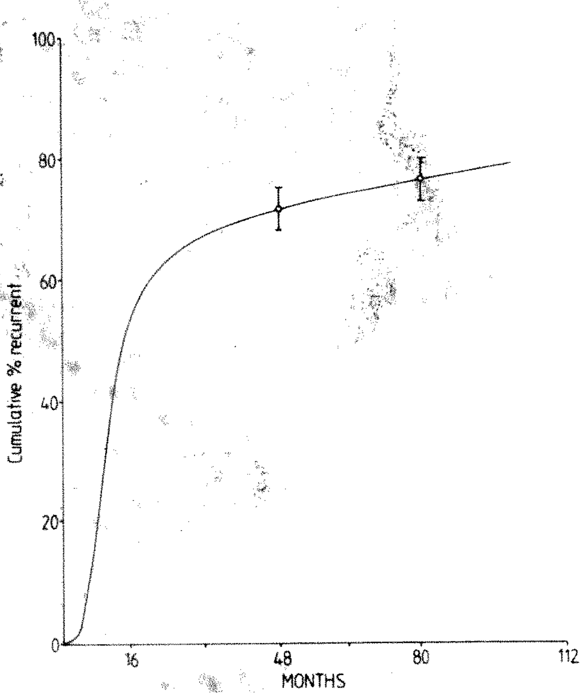

Fig. 3 T1 transitional cell carcinoma. Overall cumulative (actuarial) percentage recurrent.

was 62.8% (±5.2%) for patients who had initial complete local tumour regression and 65.5% (±5.2%) for patients showing incomplete regression ($P=0.29$).

Local tumour control. Recurrence-free rates were calculated using an actuarial (life-table) method. At the end of December 1983, 137 patients (72.1%) either had residual or recurrent tumour. The overall recurrence-free rate at 2 years was 33.9% (±3.5%) and at 5 years it was 27.7% (±3.5%). This has been expressed as the cumulative percentage with recurrence in Figure 3.

Most of the 137 patients with residual or recurrent tumours subsequently had further local treatment. Sixty-four patients (46.7%) were managed endoscopically, 35 patients (25.5%) underwent cystectomy and seven (5.1%) had a course of intravesical chemotherapy. For the small group of patients treated by cystectomy, the actuarial 5-year survival rate was 88.6% (±5.4%) and 36.7% (±14.8%) at 10 years. In the group of patients selected to be subsequently managed endoscopically the 5-year survival rate was 63.2% (±6.3%) and 34.7% (±8.1%) at 10 years.

Histological grade, number of tumours and local tumour control. Lasting local tumour control was poor in patients with grade 1 cancers. Only 16% of patients with grade 1 cancers had durable local tumour control 5 years after radiotherapy, as did 29% of those with grade 2 cancers. By contrast, 56% of patients with grade 3 cancers had durable local control 5 and 10 years after radiotherapy (Table 4). There was a significant difference in the cumulative percentage of patients with recurrence by histological grade ($P=0.0001$) (Fig. 4).

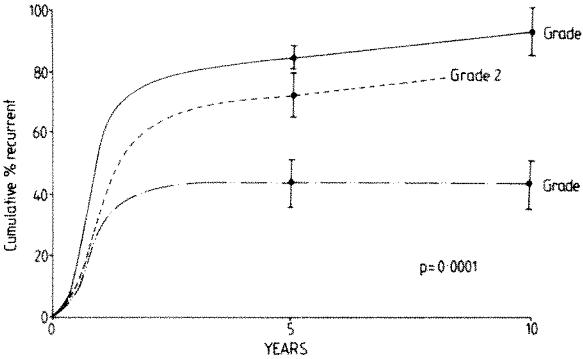

Fig. 4 T1 transitional cell carcinoma. Cumulative percentage recurrent by histological grade (Generalised savage (Mantel-Cox) test) ($P=0.0001$)

Table 6 Metastasis-free Rates by Histological Grade in Patients with Complete Local Regression

Histological grade	*Nos.*	*Number developing metastases by December 1983*	*Actuarial % metastasis-free at 5 years (± SE)*
Grade 1	29	4	89.9% (±7.0)
Grade 2	19	3	81.4% (±9.9)
Grade 3	21	2	85.4% (±9.5)
Total	69	9	

Lasting local control was slightly better in patients with a solitary cancer. Five years after radiotherapy 35% of patients with a solitary cancer had durable local control compared with 23% of those with multiple tumours and 21% of those whose tumour was diffuse (Table 4). The difference in control was not statistically significant ($P=0.25$).

Metastases. The records provided good documentation of the presence or absence of metastases in 180 of the 190 patients. The proportion of patients who remained free of distant metastases (actuarial calculation) at 5 years was 84.3% (±3.0%) and 63.2% (±9.6%) at 10 years.

For patients who had complete tumour regression there was no difference in metastasis-free rates by histological grade ($P=0.643$) (Table 6).

Discussion

The poor results of radiotherapy in the treatment of superficial, well differentiated bladder cancer have been documented for over 20 years. Almost all patients with T1 cancers will ultimately develop new lesions or recurrences (Rubin, 1961). In a review of 25 years' experience, Buschke and Jack (1967) concluded that the papillary carcinoma, grade 1, responded poorly to doses that could be given safely by external beam irradiation.

However, patients continue to be referred for radiotherapy with multiple, recurrent, well differentiated T1 cancers that have proved to be refractory to endoscopic resection with or without intravesical chemotherapy. Many of these patients are considered unfit for cystectomy because of their general medical condition or age. Patients with well differentiated T1 cancers have a good survival after radiotherapy but it is doubtful whether, in fact, radiotherapy contributes anything worthwhile to their management.

In this review 33.0% of patients with well differentiated cancers had complete local tumour regression following radiotherapy. At 5 years only 16% of patients with grade 1 cancers remained free of local recurrence, although their uncorrected survival rate was 64.5%. The proportion with persistent local control without additional treatment fell to 7.5% at 10 years. Persistent local control was slightly better in patients with a solitary tumour, which were found to be more often grade 3 than grade 2 or grade 1 histology in this series.

Patients with T1 cancers that are poorly differentiated (grade 3) are known to have a poor survival and local recurrence rates are high. In a series reported from the Royal Marsden Hospital, 9 of 69 patients managed by endoscopic resection or diathermy had grade 3, T1 cancers (Pocock *et al.*, 1982). Only one of these patients was alive at 5 years and that was following a cystectomy. Five had died of bladder cancer, one of intercurrent disease and two others had a follow-up of less than a year. The actuarial survival was less than 20% at 5 years. In another report of the results of TUR for T1 cancers, both the risk of subsequent muscle invasion and of developing metastases was related to poor histological differentiation (Heney *et al.*, 1983). They reported only 20% of patients with grade 3 cancers alive and disease-free at 3 years.

This review has demonstrated significantly better local tumour control following radiotherapy of T1 and pT1 cancers, grade 3, compared with grade 1 tumours. At 5 years 55.6% of patients with grade 3 cancers had persisting local control, having had no further treatment. No patient with grade 3 cancer had either local recurrence or developed distant metastases between 5 and 10 years after radiotherapy, suggesting that these were long-term "cures". This was also demonstrated in a series of patients with category T1 bladder cancers treated in Rotterdam.

The high probability of local recurrence in those with poorly differentiated cancers treated by TUR was not seen in those patients treated by a radium implant (Van der Werf-Messing and Hop, 1981).

There was no significant difference in this series in the survival probability following radiotherapy of patients with T1 cancers by histological grade. However, it has been demonstrated that patients with grade 3 cancers managed by TUR have a significantly poorer survival than those with grade 1 cancers (Pocock *et al.*, 1982; Heney *et al.*, 1983).

Patients who achieved complete local tumour regression after radiotherapy had a similar probability of developing distant metastases irrespective of histological grade. This again is in marked contrast to the natural history of patients treated by TUR, after which those with grade 3 cancers had a greater risk of developing metastases (Van der Werf-Messing and Hop, 1981; Heney *et al.*, 1983).

The management of superficial bladder cancers continues to pose problems. Radiotherapy offers little prospect of control for T1 cancers of histological grades 1 and 2. Radical radiotherapy offers a high probability of long-term local control for grade 3 superficial (T1) transitional cell carcinomas of the bladder. Radiotherapy would appear to reduce the risk of subsequent metastases in those who achieve complete local regression of bladder cancer and so improve their prognosis. Radical small field beam directed radiotherapy is commended as the treatment of choice for patients with poorly differentiated transitional cell carcinoma of the bladder classified as T1 or pT1.

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The Authors

P. M. Quilty, FRCR, Lecturer and Honorary Senior Registrar.

W. Duncan, DMRT, FRCR, FRCP, FRCS, Professor of Radiotherapy.

Requests for reprints to: P. M. Quilty, Department of Clinical Oncology, Western General Hospital, Edinburgh EH4 2XU.

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Coincident Vesical Transitional Cell Carcinoma and Prostatic Carcinoma

Clinical Features and Treatment

P. A. ANDROULAKAKIS, H. M. SCHNEIDER, G. H. JACOBI and R. HOHENFELLNER

Department of Urology, University of Mainz Medical School, Mainz, Federal Republic of Germany

Summary—Twenty-two patients with vesical urothelial carcinoma associated with prostatic carcinoma were reviewed. They represented 1.5% of the bladder and prostatic tumours treated in our department wihin a 12-year period from 1968 to 1979. Their management included several treatment policies, based on the separate assessment of each tumour variant. For non-infiltrating bladder tumours, transurethral tumour resection was combined with hormonal treatment, external radiotherapy or resection of the prostate depending on the stage of the prostatic tumour. Radical cystoprostatectomy was performed for two cases of infiltrating bladder tumour with well localised prostatic tumours. A conservative primary approach seems justifiable in the management of double carcinoma of the bladder and prostate. The coincidence of bladder urothelial carcinoma and prostatic carcinoma *per se* is not an adverse prognostic factor; prognosis is more closely related to the pathological stage and grade of the bladder tumour. Cystoprostatectomy for patients with infiltrating bladder tumours could be curative, in selected cases, for the prostatic cancer as well.

The term "double carcinoma" of the bladder and prostate implies the coincidence of bladder urothelial carcinoma and prostatic carcinoma in the same patient (Fig). This combination represents a clinical entity which should not be confused with other tumour variants of the prostatovesical region, such as transitional cell carcinoma of the prostate.

Problems concerning patients with double carcinoma of the bladder and prostate have not been sufficiently documented (Ward-McQuaid, 1963). This study was undertaken in an attempt to determine the incidence of true double carcinomas, the problems possibly arising from combined management of the bladder and prostatic tumours, and the best treatment.

Patients and Methods

Between 1968 and 1979, 75 patients were initially diagnosed as having double carcinoma of the bladder and prostate. Following review of their histopathological data, 53 patients had to be excluded because they represented false cases of double carcinoma. Thus, patients with transitional cell bladder tumours with secondary involvement of the prostate, prostatic transitional cell (intraductal) carcinomas extending to the bladder or prostatovesical tumours of poorly defined site of origin because of dedifferentiation, were excluded from this study. The remaining 22 patients, who had a bladder urothelial carcinoma associated with prostatic carcinoma, were available for analysis. For definitive histological diagnosis, a bladder TUR specimen and prostatic TUR specimen or transrectal punch biopsy material was available.

The patients' ages ranged from 55 to 87 years (median 69) and the most common presenting symptoms were gross haematuria and dysuria. In 12 patients both tumours were discovered at the same time; in the other 10 cases the time interval between the first and second diagnosis ranged from 6 months to 3 years; prostatic carcinoma was diag-

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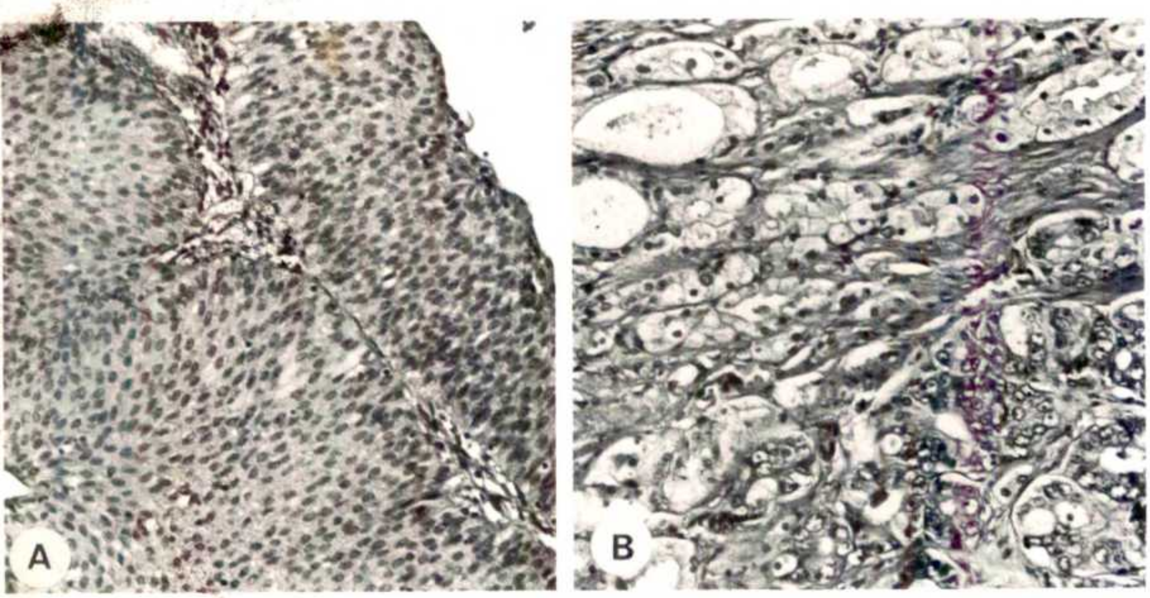

Fig. Typical double carcinoma of bladder and prostate: transitional cell bladder carcinoma (A) (H and E × 100) associated with prostatic carcinoma (B) (H and E × 400).

nosed first in six cases, while the opposite occurred in four cases. After excluding one patient lost to follow-up, 21 patients with a follow-up of up to 13 years (mean 5) remained for further analysis.

Treatment Treatment strategies were based on the assessment of each tumour variant, *i.e.* bladder tumour and prostatic tumour, separately. On the basis of their management our patients could be divided into four groups (Table):

Group I: Primary local resection ($n = 19$)

Nine patients underwent transurethral resection of both bladder and prostate tumours. All had non-infiltrating bladder tumours. Three received further treatment for the transitional cell tumours with Adriamycin instillations. In five cases the prostatic carcinoma was an incidental finding and no further treatment was undertaken. In the other four patients with clinical T1 and T2 lesions, low dose oestrogen treatment, equivalent to 1 mg stilboestrol daily, was given.

Ten more patients with non-infiltrating bladder tumours were treated by transurethral resection of the bladder tumour alone; four received additional Adriamycin instillations as prophylaxis for recurrences. The parallel management of their prostatic tumours is outlined below (groups II and III).

Group II: Radiotherapy ($n = 5$)

External high voltage radiotherapy with curative intent was reserved for the treatment of four patients with localised (T1-T2) prostatic tumours; the tumour dose was 7600 rads. Two patients were given oestrogens additionally after relapse 2 years later. One further patient, who had been subjected to repeated unsuccessful transurethral resections of a bladder tumour and who developed prostatic cancer 2 years later, received external radiotherapy with modified extended fields for both tumours.

Group III: Primary endocrine treatment ($n = 5$)

Hormonal management of patients with locally advanced or metastatic prostatic tumours was given in the form of oestrogens (3), castration (2) or cyproterone acetate (1).

Group IV: Radical surgery ($n = 2$)

Cystoprostatectomy as the primary mode of treatment was performed in a 58-year-old patient in whom the bladder and prostatic tumours were diagnosed at the same time; he had an infiltrating (pT3) bladder carcinoma with a small (T1) prostatic tumour, negative lymph nodes at pelvic lymphadenectomy and no distant metastases. The second patient had an infiltrating, poorly differentiated (pT2) bladder carcinoma with several recurrences after transurethral resection; when he developed prostatic cancer (T2) 1 year later, cystoprostatectomy was performed to remove both tumours.

Table Treatment Policies in Patients with Double Carcinoma of Urinary Bladder and Prostate

	Therapy	*Tumour characteristics*
	Group I Local primary resection (n = 19)	TUR (n = 9) Bladder, pT1,2 (n = 9)* → pT3 (n = 2) Prostate, T0 (n = 5); T1,2 (n = 4)**
		TUR (n = 10) Bladder, pT1,2 (n = 10)* → pT3 (n = 3)
Group II Local radiotherapy (n = 5)	P-Ca. T1,2 (n = 4) → Relapse (n = 2)**	
	P-Ca. (T2) B-Ca. (pT3) extended field (n = 1)	
	Group III Primary endocrine therapy (n = 5)	P-Ca. T3,4 N0-4 M0,1 —oestrogens (n = 3) —orchiectomy (n = 2) —orchiectomy + cyproterone acetate (n = 1)
Group IV Radical surgery (n = 2)	—B-Ca. pT3 and P-Ca. T1 (n = 1) —B-Ca. pT2 and P-Ca. T2 (n = 1)	

* Adjunct Adriamycin instillation prophylaxis
** Adjunct oestrogen therapy

Results

There were no major problems in carrying out the combined therapeutic policies and follow-up in our patients with double carcinoma of the bladder and prostate.

Transurethral resection, combined with intravesical instillation of Adriamycin in some cases, was the treatment of choice for non-infiltrating bladder tumours and could be combined very effectively with various therapeutic policies for the management of the associated prostatic cancer. Deeply infiltrating bladder cancer was best treated by radical cystoprostatectomy.

Patients with localised, intraprostatic (T1-T2) tumours responded well to external radiotherapy. Histopathological control of the prostate in three of them after 24, 28 and 36 months respectively, showed no evidence of malignancy. Transurethral resection of the prostate, alone or in combination with low dose oestrogens, was sufficient for incidental carcinoma of the prostate with respect to local tumour control.

During the follow-up period five patients died from progressive or metastatic cancer of the bladder or prostate. Three had developed deeply infiltrating (pT3) bladder neoplasms with localised, well differentiated prostatic tumours; one had a locally advanced (T3) prostatic tumour associated with a non-infiltrating bladder tumour and one had a deeply infiltrating bladder tumour associated with a T3 prostatic carcinoma.

Five other patients died of unrelated causes; three showed no evidence of disease at that time. Of the 11 patients remaining alive at the completion of this study, two with infiltrating bladder tumours and one with a non-infiltrating but poorly differentiated bladder carcinoma showed evidence of progressive or metastatic bladder cancer.

Discussion

Double carcinoma represented 2.6% of 845 bladder tumours, 3.6% of 604 prostatic tumours or 1.5% of a total of 1449 cases of bladder and prostatic tumours treated in this department between 1968 and 1979.

A precise histopathological diagnosis is the first and most important step in dealing with the various prostatovesical tumours (Melicow and Uson, 1976). Transitional cell carcinomas involving both bladder and prostate may give the impression of a double carcinoma. Since they carry an unfavourable prognosis, these tumours must be treated aggressively (Greene *et al.*, 1973; Kirk *et al.*, 1979; Wolfe and Lloyd-Davies, 1981).

The coexistence of a bladder urothelial carcinoma with prostatic carcinoma does not carry *per se* an unfavourable prognosis. Progress depends on the characteristics of each tumour separately. Of the eight patients who, at the end of our study, had either died of (5) or showed evidence of progressive bladder or prostatic cancer (3), six had an infiltrating (pT3) bladder tumour and two a locally extensive (T3, T4) prostatic tumour. Of 13 patients with non-infiltrating bladder tumours, only one (with a high grade tumour) showed evidence of progressive bladder cancer.

Despite the limited number of cases, it appears that the pathological staging of a bladder cancer is a more important prognostic factor than the stage and grade of its prostatic counterpart, and this must be taken into consideration in planning management.

Considering their management, our patients with coincident bladder and prostatic carcinoma could be divided into four major groups (Table). Of relevance to their treatment selection was the synchronous or metachronous diagnosis of both tumours. Simultaneous diagnosis enabled us to follow a more rational plan of treatment for both tumours. In tumours with metachronous appearance it was not possible to follow a similar policy from the beginning. Initially their management was more individually orientated, but during the course of the disease the tendency was to integrate into a common plan of treatment the therapeutic approach for each tumour.

The two patients with deeply infiltrating bladder tumours subjected to radical cystoprostatectomy were alive 8 and 13 years post-operatively without evidence of disease. Of the other six patients who had infiltrating bladder neoplasms but were not treated radically, four had died of and two had evidence of progressive bladder cancer.

Our observations seem to confirm the need for aggressive treatment in infiltrating bladder carcinoma (Wallace and Bloom, 1976; Hall and Heath, 1981). Patients with double carcinoma of the bladder and prostate, with an infiltrating bladder lesion, should be considered candidates for radical surgery; cystoprostatectomy could have a double curative effect as well in patients with localised intraprostatic tumours.

If there are contraindications to radical surgery, high voltage radiotherapy with modified fields to include both the bladder and prostate tumour sites should be considered as the alternative policy in patients with infiltrating bladder neoplasms and localised prostatic tumours. Patients with advanced prostatic cancer and non-infiltrating bladder tumours can be adequately treated with hormonal management combined with transurethral bladder surgery.

Our data suggest that double carcinomas of the bladder and prostate are a relatively rare entity. In more than 50% of the cases, both tumours are discovered simultaneously. It is possible to treat each tumour on its own merit, without particular problems arising from the combined therapeutic and follow-up strategies. Radical surgery should be considered a prime indication in the presence of infiltrating (pT3) bladder carcinoma and, in selected cases, can have a curative effect upon the prostatic tumour as well.

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The Authors

P. A. Androulakakis, MD, formerly Fellow in Urology, University of Mainz Medical School. Now Consultant Urologist, Aghia Sophia Children's Hospital, Athens, Greece.

H. M. Schneider, MD, Honorary Lecturer, Institute of Pathology, University of Mainz Medical School.

G. H. Jacobi, MD, Professor, Department of Urology, University of Mainz Medical School.

R. Hohenfellner, MD, Professor and Chairman, Department of Urology, University of Mainz Medical School.

Requests for reprints to: P. A. Androulakakis, 14a Ioannou Gennadiou Street, GR-11521 Athens, Greece.

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Prostatic Commissurotomy

A Simple Technique for the Treatment of Benign Prostatic Hypertrophy

A. SHAFIK

Department of Surgery, Cairo University, Cairo, Egypt

Summary—Division of the anterior prostatic commissure and the bladder neck (but sparing the mucosa) achieves "urethral decompression". This simple technique for the treatment of benign prostatic hypertrophy was performed in 68 poor risk patients.

The results were very satisfactory, especially in large prostates with lateral lobe enlargement. No patient required blood transfusion. Immediate and late post-operative complications were not encountered and the hospital stay was short. The obstructive manifestations and the maximal urinary flow rate improved in 91% of patients. Failures were due to incomplete prostatic commissurotomy.

Many techniques have been devised for the treatment of benign prostatic hypertrophy. They aim at relieving urethral obstruction rather than actually removing prostatic tissue, which often leads to complications.

Cystomyotomy was described by Shafik (1973) for the relief of bladder neck obstruction. The results in more than 350 cases of bladder neck obstruction due mainly to bilharziasis were so impressive that a similar technique has been used for the treatment of obstructing benign prostatic hypertrophy. This report embodies the results of this technique.

Patients and Methods

The series comprised 68 patients with benign prostatic hypertrophy (age range 68-86 years). The lateral lobes were enlarged in 57 patients and the middle lobe in 11. Most were poor risk patients (Table 1), including some with a recent cardiac infarct or stroke. There were three patients with implanted cardiac pacemakers. Many were on catheter drainage. In three patients the blood urea exceeded 25 mmol/l.

Table 1 Associated Systemic Conditions in 68 Patients with Benign Prostatic Hypertrophy

	No. of patients
Severe cardiac decompensation	27
Cerebrovascular accident	3
Diabetes	32
Severe arthritis	2
Paralysis agitans	1
Bronchial asthma	3

The patients were subjected to routine pre-operative examination and investigations, including urine analysis, blood urea nitrogen, intravenous urography and cysto-urethrography. Cysto-urethroscopy showed trabeculation, saccules or diverticula in all patients. It also demonstrated intra-urethral lateral lobe prostatic hyperplasia or intravesical middle lobe enlargement. The patients were also assessed by urodynamic studies consisting of measurement of the free urinary flow rate. These studies were repeated 3 months post-operatively and every 6 to 12 months thereafter.

Indications for operation are shown in Table 2 and associated urological conditions in Table 3. Sixty-two per cent of the patients had acute retention and the remainder were subjected to surgery because of their obstructive symptoms and intra-

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Table 2 Indications for Operation

	No. of patients
Acute retention	42
Chronic retention	8
Symptoms of obstruction	18

Table 3 Associated Urological Conditions

	No. of patients
Bladder calculi	4
Bladder diverticula	2
Pre-operative azotaemia	13
Pyelonephritis	4

venous urographic and uroflowmetric findings. Pre-operative catheter drainage was used when there was a large amount of residual urine or when the patient was admitted in acute urinary retention.

Technique

The patient is placed in a recumbent position. The bladder neck is exposed retropubically through a midline sub-umbilical incision (Fig. 1A). A broad Deaver retractor depresses the bladder and brings the bladder neck and prostate into view. The loose areolar and fatty tissue is gently dissected away and large veins are coagulated and transected until the prostatic capsule is well defined.

A longitudinal incision is made in the midline of the bladder, starting 1.5 cm above the bladder neck and extending down to the upper end of the prostatic commissure (Fig. 1A). The incision is carried out through the muscle coat, sparing the mucous membrane (Fig. 1B). The tip of a long curved clamp is then entered between the prostatic urethral mucosa and the commissure (Fig. 1C). By repeated opening and closing of the clamp jaws, the urethral mucosa is separated from the commissure, taking care not to injure the mucosa. Two clamps are applied to the commissure 0.5 cm from either side of the midline and the commissure is divided between them (Fig. 1D). The urethral mucosa is further dissected from the undersurface of the divided commissure ends until it bulges freely between them. The cut ends are then transfixed with 2/0 chromic catgut stitches (Fig. 1E). The bulging mucosal cuff should include the mucosa of the bladder neck and the urethra. Some dissection may be necessary to ensure that all constricting tissue has been severed and that efficient patency has been achieved. Accidental mucosal perforation, which would show from spontaneous urinary leakage or with a control compression of the unopened bladder, is sutured with 4/0 chromic catgut.

Should opening of the bladder be indicated in the course of the operation (because of a stone or other lesion), a finger should be passed through the bladder neck to gauge its patency, to assist further bulging of the mucous membrane and to clarify any constricting fibres.

After securing haemostasis, the pre-vesical space is drained, a urethral catheter is introduced in the urinary bladder and the abdominal wound is closed.

No patient required blood transfusion during or after the operation. The urethral catheter was removed on the second post-operative day and the suprapublic catheter, if present, was removed on the fifth post-operative day.

Results

Convalescence was smooth in all patients. Post-operative bleeding was not encountered. In the six patients in whom the bladder was opened for removal of stones or diverticula (Table 3), healing of the wound was satisfactory after removal of the suprapubic catheter; no suprapubic fistula occurred. Improved voiding was achieved in 62 of the 68 cases. Nocturia was eliminated in 38 patients; 24 have mild nocturnal frequency (once or twice nightly) and six void more than twice nightly.

The maximal urinary flow rate was below the normal range before surgery in all patients and increased afterwards in 62 of the 68 patients. In 56 patients, eight of whom had middle lobe enlargement, the increase was enough to bring the flow into the normal accepted range (Drach and Binard, 1976; Abrams and Torrens, 1979). In another six patients the flow rate was above the upper range of normal. The best results were obtained with huge prostates in which the obstructing tissue was estimated to weigh more than 60 g. Six patients, three of whom had middle lobe enlargement, remained within the range described for prostatic patients. Their obstructive manifestations showed minimal improvement. Cysto-urethroscopy showed urethral indentation which indicated the presence of residual obstruction due to incomplete division of the prostatic commmissure. Repeated urethral dilatation resulted in improvement of the symptoms and the maximal urinary flow rate but not to the normal range. Table 4 shows the average resi-

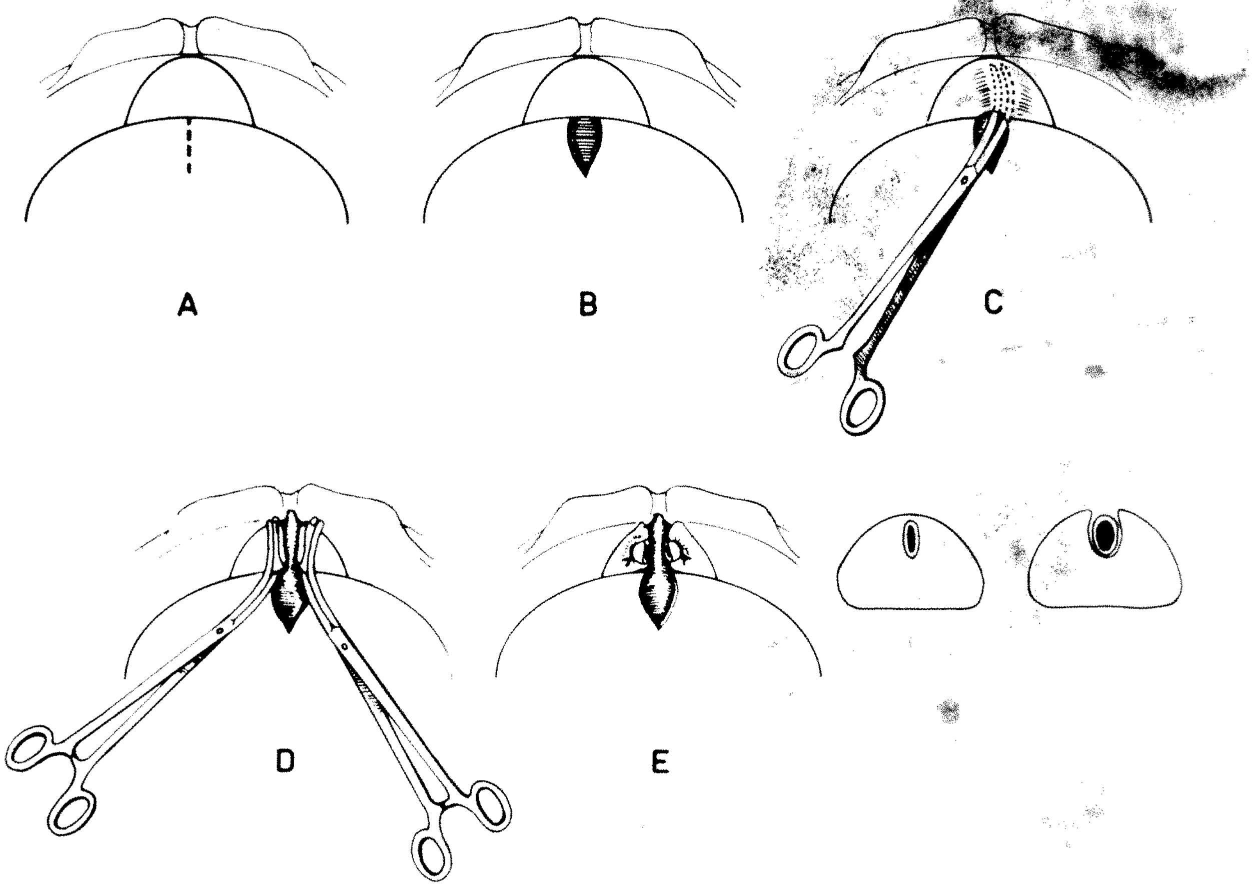

Fig. Diagram illustrating prostatic commissurotomy.

Table 4 Average Residual Urine before and after Commissurotomy in 68 Patients

	Residual urine (ml)
Pre-operative	185 (Range 60-760)
Post-operative	40 (0-90)

dual urine before and after surgery in the 68 patients. It demonstrates a significant post-operative reduction in volume.

Ejaculation was not affected and epididymitis did not occur. Cystograms and voiding cysto-urethrography showed lowering of the bladder base, normal urethral calibre and improved funnelling of the proximal urethra. There has been no urethral stricture or incontinence. The 48 patients who were available for follow-up between 2 and 5 years had no recurrence of symptoms.

Discussion

The present results demonstrate the effectiveness of the technique in the treatment of benign prostatic hypertrophy. Satisfactory results were obtained in 54 of 57 patients with predominantly lateral lobe enlargement and in 8 of 11 patients with middle lobe enlargement. There were no complications during or after operation and no patient required blood transfusion. Uroflowmetric studies showed improvement in the maximal urinary flow rate in 91% of cases. This could result from either hypertrophied detrusor muscle or improved funnelling of the proximal urethra after prostatic commissurotomy. The six patients (9%) who showed no uroflowmetric or symptomatic improvement entered the study in its early stage.

The improvement achieved with the present technique is attributable to the release of the urethra from the constricting action of the hypertrophied prostatic tissue by division of the anterior commissure, which is easily dissected from the prostatic urethra. The procedure thus achieves "urethral decompression", which is the aim of any prostatectomy for benign hypertrophy.

The operation has several advantages over prostatectomy. The procedure itself is short and technically easy. The patients' stay in hospital is relatively brief and blood loss is minimal, an important consideration in view of age-related complications. Post-operative urethral stricture, which occurs in 6% of patients after transurethral prostatectomy (Mebust *et al.*, 1979), did not occur in this series. This is because the urethral mucosal tube is kept intact in commissurotomy. Urinary incontinence did not occur because there was no interference with the urethra and its musculature.

It could be argued that the operation leaves the adenomatous tissue liable to malignant transformation, but the relationship between benign prostatic hypertrophy and prostatic cancer is a matter of controversy and, according to Rotkin (1976), should be held in abeyance until more evidence is available.

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The Author

A. Shafik, MD, Professor of Surgery, Faculty of Medicine, University of Cairo.

Requests for reprints to: A. Shafik, 2 Talaat Harb Street, Cairo, Egypt.

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Factors Influencing Post-operative Hospital Stay after Transurethral Resection of the Prostate Gland

R. L. WOLVERSON, A. R. E. BLACKLOCK, J. R. GEDDES and A. O'HAGAN

Department of Urology, Walsgrave Hospital and Department of Statistics, University of Warwick, Coventry

Summary—The influence of 12 clinical and social factors on the length of post-operative stay in hospital after transurethral resection of the prostate was investigated in 100 patients. Using a multiple binary regression analysis, the factors significantly associated with a post-operative stay exceeding 6 days were: patient's age >70 years ($P < 0.005$), the presence of existing cardiovascular disease ($P < 0.005$) and the weight of the prostate gland resected >10 g ($P < 0.005$). The first two factors are useful in providing a prediction of prolonged post-operative stay. The results indicate that those factors associated with a prolonged post-operative stay are beyond the control of the clinician.

Transurethral resection of the prostate gland is the commonest major urological procedure. In this unit approximately 500 operations are carried out per year and over 90% are transurethral procedures. Therefore any factors which significantly increase the cost of these procedures should receive close scrutiny. The aim of this survey was to analyse the influence of 12 clinical and social factors on the length of post-operative stay and to determine whether it could be reduced and thus make our hospital beds more cost effective. So few open prostatectomies are performed that the economics of this procedure were not studied.

Patients and Methods

A retrospective study was carried out on 100 patients who had undergone transurethral resection of the prostate between January 1983 and January 1984. The clinical and social factors examined were as follows:

1. Age of patient: <60 years (10 patients), 60 to 70 years (36), >70 years (54).
2. Pre-operative duration of symptoms: >6 months (88), <6 months (12)
3. Coexistent pre-operative medical conditions: musculoskeletal disease (12), cardiovascular disease (29), respiratory disease (12), colorectal surgery (2).
4. Admission to hospital: emergency (22), elective (78).
5. Histology of prostate: benign (86), malignant (14).
6. Per-operative blood loss: >1 litre (50), <1 litre (50).
7. Duration of pre-operative admission: <6 days (82), >6 days (18).
8. Post-operative urinary infection (18).
9. Duration of post-operative stay: <6 days (42), >6 days (58).
10. Weight of prostate resected: <10 g (26), 10 to 20 g (44), >20 g (30).
11. Patient lives alone (21).
12. Operator, consultant only (42).

Statistical Methods

The response variable was binary, *i.e.* whether or not a patient's post-operative stay exceeded 6 days. We explored the dependence of the response variable on the 12 factors using the computer package GLIM. This package performs statistical analysis using Generalised Linear Models and allows thorough exploration of the ways in which factors

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may affect, singly or in combination, the response variable. Statistical analysis with GLIM is a standard and extensively used technique. Technical details are as follows (further details and the original data are available from the authors on request):

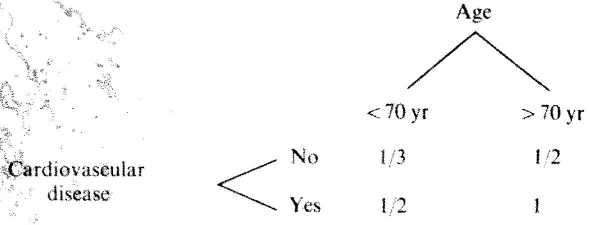
The link function used was the logistic link, as is generally appropriate to binary data of this form. Lindley (1964) gave a Bayesian interpretation to GLIM analysis with the logistic link and this permits a more direct interpretation of significant probabilities. As a check on the choice of link, the complementary log-log link was tried and found to give essentially identical conclusions. Model fitting involved searching for best-fitting subsets of effects and interactions. The selected model contained just three main effects. This model accounted for deviance of 31.8 on 3 df, which is highly significant. A fourth factor was found to be significant (reducing deviance by 8.4 on 1 df) but was not included for reasons given in the next paragraph. The chosen model fitted the data well, one indicator of which is that the residual deviance is 105 on 95 df, giving a residual mean deviance close to 1.

In less technical terms, the findings of the analysis were as follows. Of the 12 original factors, eight were eliminated as having no significant effect at all. Another factor, the presence or absence of existing respiratory disease, was rejected because, although it had a fairly significant effect, the effect was counter-intuitive. Medical and commonsense reasons dictate that if this factor were to have an effect it should be positive (*i.e.* presence of respiratory disease should increase the chance of a long post-operative stay), whereas the data suggested a negative effect. The three remaining factors were found to have significant and plausible effects. Both age and weight of resection were originally analysed as three-level factors, but equally good fit was achieved by collapsing them to two levels each (greater or less than 70 years, greater or less than 10 g resection). We therefore concluded that all three factors had real effects on the response variable, with probability exceeding 0.995 ($P<0.005$) in each case.

In addition to testing hypotheses, the analysis yielded parameter estimates which could be used to give predictive probabilities for length of stay. The most useful predictive probabilities would be prior to admission, when one of the significant factors (weight of resection) would be unknown. Approximate predictive probabilities based on the two available factors are shown in the Figure.

Results

The results of the statistical analysis showed that when each individual factor was analysed in conjunction with the other factors, the factors associated with a post-operative stay exceeding 6 days were:



		< 70 yr	> 70 yr
Cardiovascular disease	No	1/3	1/2
	Yes	1/2	1

Fig. Approximate predictive probabilities. Each value is the probability that a patient with the given age ± cardiovascular disease characteristics will require a post-operative stay exceeding 6 days.

(1) Age >70 years ($P < 0.005$).
(2) Concomitant cardiovascular disease ($P < 0.005$).
(3) Weight of prostate gland resected >10 g ($P < 0.005$).

Age and cardiovascular disease were found to be useful predictors of a prolonged hospital stay (Fig.). It can be seen that the chance of prolonged hospitalization for a patient aged 70+ years with concomitant cardiovascular disease is 100% and without cardiovascular disease is 50%.

Discussion

The data were examined by a multiple binary regression analysis. This method ensures that a single factor is not evaluated in isolation, but in relation to all of the other variables which have been collected and analysed. It has previously been shown that the duration of hospital stay is the single most important determinant of cost (Arabi *et al.*, 1980).

It is possible that factors not directly related to the patient's medical condition could have been responsible for a prolonged hospital stay. For instance, if a patient lives alone, convalescence in hospital may be necessary while the Social Services are being mobilised. Similarly, the skill and experience of the surgeon could be related to hospital morbidity and thus the length of hospitalisation. Neither of these factors was shown to be significant in prolonging hospital admission but the three factors that were associated with the length of stay (age of patient, concomitant cardiovascular disease and weight of prostate gland resected) are beyond the control of the clinician.

Thus it appears that the duration of hospital stay after transurethral resection of the prostate, being the single most important determinant of cost, is unlikely to be reduced.

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The Authors

R. L. Wolverson, FRCS, Senior Urological Registrar, Walsgrave Hospital.

A. R. E. Blacklock, FRCS, Consultant Urologist, Walsgrave Hospital.

J. R. Geddes, FRCS, Consultant Urologist, Walsgrave Hospital.

A. O'Hagan, BSc, PhD, Lecturer, Department of Statistics, University of Warwick.

Requests for reprints to: A. R. E. Blacklock, Department of Urology, Walsgrave Hospital, Clifford Bridge Road, Walsgrave, Coventry CV2 2DX.

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Incidental Carcinoma of the Prostate: Factors Influencing Prognosis

A. AKDAS, H. A. ÖZEN, I. TUNCER, C. TASAR and D. REMZI

Departments of Urology and Pathology, Hacettepe Univeristy, Ankara, Turkey

Summary—Thirty-four patients with TO carcinoma of the prostate were revived in an attempt to correlate their clinical progress with the histopathological features of the tumour at presentation. Two different grading systems were used. It was found that no matter which system was used, the poorer the histopathological grade the poorer the prognosis.

Despite the many recent studies on prostatic carcinoma there is still debate regarding definition, significance and treatment of incidentally discovered TO carcinoma of the prostate. This group should not be underestimated, since it comprises at least 10% of all cases of prostatic carcinoma (Heaney *et al.*, 1977) and is observed in 6 to 10% of all patients undergoing prostatectomy for benign prostatic hyperplasia (Denton *et al.*, 1965; Varkarakis *et al.*, 1970; Khalifa and Jarman, 1976).

The long natural history of this disease has often led to a policy of conservative treatment (Byar, 1977) but metastases may develop even in patients with small tumours (Kern, 1978; Beynon *et al.*, 1983b).

The purpose of this study was to examine the relationship between histopathological findings and the prognosis of the disease in patients with TO prostatic carcinoma.

Patients and Methods

We reviewed the records of 356 consecutive patients with prostatic carcinoma presenting at this hospital between 1968 and 1982. During this period 34 patients were diagnosed as having TO prostatic carcinoma, which may be defined as clinically unrecognised prostatic cancer. None of these patients had evidence of prostatic carcinoma on physical examination, on serum acid and alkaline phosphatase estimations, radiographic studies of the chest, skeleton and urinary tract, and isotopic bone scan. The original specimens and histopathological slides were reviewed by a single investigator (I.T.), who had no knowledge of the patient's prognosis.

The diagnosis was confirmed in all cases and the slides were re-evaluated with special emphasis on the number of foci, stromal reaction, perineural infiltration and eventually the differentiation of the tumour. The tumours were graded in two ways; according to the classification of Gleason and Mellinger (1974) and also according to whether they were well, moderately or poorly differentiated (McCullough *et al.*, 1974). Out-patient follow-up was carried out at 3-monthly intervals with clinical examination, full blood count and estimations of prostatic acid phosphatase and alkaline phosphatase. In addition, isotopic bone scans were repeated at 6-monthly intervals.

Results

All tumours were classified as TO MO. The patients' ages ranged from 61 to 87 years (average 69.8) and length of follow-up ranged from 26 to 142 months (average 32.6).

Of the 34 TO patients, 14 received various kinds of hormonal treatment initially. Deferred treatment with regular follow-up was our policy in the remaining 20 patients and it was with this group

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Table 1 Relationship between Progression of Disease and Mean Gleason Score

	Number of patients	*Mean Gleason score*
Died	7	6.43
Alive with evidence of cancer	6	5.50
Alive without evidence of cancer	7	3.00
Total	20	

that the study was mainly concerned. The correlation between the mean Gleason score and subsequent disease progression is shown in Table 1, where it can be seen that those who died and those who were alive with disease had worse mean scores than those who were alive without evidence of disease. None of the patients with poorly differentiated tumours was alive in the study period, whereas only 11.1% of the well differentiated cases died in the same period (Table 2).

Perineural infiltration by tumour and subsequent progression of the disease were also investigated. Forty per cent of the patients had perineural infiltration and 62.5% died of cancer. Although 16.6% without involvement of the nerve sheaths died in the same period, the mean Gleason score in the latter group was 3.5, in contrast to 7.13 in the first group (Table 3). In only two patients was prostatic carcinoma detected in less than three foci. The rest were regarded as diffuse carcinoma.

Discussion

The currently accepted management of TO carcinoma of the prostate encompasses a wide range of treatments. These include radical surgery, radiation therapy, hormonal manipulation, observation only or a combination of these treatments. Byar (1977) reported that the survival of patients with incidentally diagnosed (A stage) carcinoma of the prostate was not improved by commencing active treatment at the time of diagnosis. Many patients in this stage have a good prognosis and seldom have clinical progression of the disease (Correa *et al.*, 1974; Heaney *et al.*, 1977; Parfitt *et al.*, 1983). Unfortunately, however, some patients do have a poor prognosis in terms of survival, incidence of disease progression and nodal metastasis, and many studies have been carried out to determine the factors that influence the prognosis (Correa *et al.*, 1974; Khalifa and Jarman, 1976; Cantrell *et al.*, 1981; Beynon *et al.*, 1983a; Parfitt *et al.*, 1983).

The incidence of well, moderately and poorly differentiated tumours in T category (or stage A) was reported as 60, 40 and 32% respectively by Sheldon *et al.* (1980). In our study, 45% of the patients had well differentiated TO prostatic carcinoma. Many authors have reported a statistically significant relationship between survival rates and histopathological grading in this particular stage of the disease. In the study by Correa *et al.* (1974), only 7.7% of 39 patients with focal and well differentiated lesions had disease progression and none

Table 2 Relationship between Disease Progression and Tumour Differentiation

	Number of patients	*Died*	*Alive with evidence of disease*	*Alive without evidence of disease*
Well differentiated	9	1	1	7
Moderately differentiated	5	2	3	—
Poorly differentiated	6	4	2	—
Total	20	7	6	7

Table 3 Relationship between Perineural Infiltration and Progression of Disease

	Number of patients	*Mean Gleason score*	*Died*	*Alive with evidence of disease*	*Alive without evidence of disease*
Perineural infiltration positive	8	7.13	5	3	—
Perineural infiltration negative	12	3.50	2	3	7
Total	20				

died of cancer. Similarly, Bauer *et al.* (1960) reported a favourable outcome for patients with well differentiated tumours (71.5% survival rate) as opposed to 12.5% in those with moderately and poorly differentiated lesions. Our findings were similar to those of the above studies regarding Mostofi's classification. The correlation between the Gleason score and metastatic stage at presentation and tumour size was demonstrated by Beynon *et al.* (1983b). Our study clearly showed that the patients who died of cancer had the worst mean Gleason scores.

Involvement of the nerve sheaths by tumour was detected in 40% of cases. Although a correlation might be found between perineural infiltration and subsequent disease progression, when the patients were evaluated individually with regard to histopathological grading, it was clear that this relationship was attributable to the grade of the tumour rather than to perineural infiltration *per se* because the mean Gleason scores in these groups were 7.13 and 3.50 respectively.

Many studies, including those by Varkarakis *et al.* (1970), Cantrell *et al.* (1981) and Fan and Peng (1983), have demonstrated a strong correlation between tumour volume when first discovered and progression of disease; since most of our patients had diffuse tumours (90%), it was not possible to correlate the extent of the tumour with its biological behaviour.

In conclusion, our findings have shown that the prognosis of patients with TO prostatic carcinoma correlates well with the histological grade. No matter which grading system is used, the poorer the histological grade the poorer the prognosis. Other parameters such as extent of tumour, perineural spread, *etc*, are secondary features which may be attributable to the grade of the tumour. We were unable to study the significance of the size of the primary tumour, and this is known to be a strong prognostic factor. When deciding on treatment for incidentally diagnosed prostatic carcinoma, emphasis should be given to the histopathological grading of the tumour.

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The Authors

A. Akdas, MD, Associate Professor, Department of Urology, Hacettepe University.

H. Özen, MD, Lecturer, Department of Urology, Hacettepe University.

I. Tuncer, MD, Associate Professor, Department of Pathology, Cukurova University.

C. Tasar, MD, Associate Professor, Department of Urology, Hacettepe University.

D. Remzi, MD, Professor and Chairman, Department of Urology, Hacettepe University.

Requests for reprints to: A. Akdas, Department of Urology, Hacettepe University, Ankara, Turkey.

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Diagnosis and Treatment of Posterior Urethral Injury

J. W. FOWLER, G. WATSON, M. F. SMITH and J. R. MacFARLANE

Department of Urology, Royal Infirmary, Edinburgh

Summary—The initial investigation and diagnosis in 28 patients with posterior urethral trauma are presented. Twenty-five patients underwent either primary realignment for complete rupture or cystostomy alone for partial rupture. The results of their management are reported.

Posterior urethral injuries occur in 4 to 25% of patients, usually male, who sustain a fracture of the bony pelvis (Devine and Devine, 1982). In the past, after clinical diagnosis, exploration and urethral realignment by "railroading" were carried out. Mitchell (1968) and Morehouse *et al.* (1972) showed that many such injuries were partial and, if left, a proportion would heal spontaneously. They also pointed to the high complication rate which appeared to follow aggressive operative treatment.

This led to conservative management by suprapubic diversion, with delayed urethral surgery as required, being proposed as the treatment of choice for all injuries (Morehouse *et al.*, 1972). Some surgeons would accept this type of management for partial injuries only and feel realignment to be applicable for complete rupture (Cass and Gopec, 1978; Patterson *et al.*, 1983). The efficacy of any treatment can only be judged in the light of an accurate diagnosis, a feature often lacking in reports of the results of treatment for urethral injury; it is, however, unlikely that any one treatment is appropriate to the whole range of posterior urethral trauma. It seems that the reduction of separation in complete rupture by realignment, and simple suprapubic diversion in partial rupture, would be appropriate. It has therefore been our policy to investigate those patients with a fractured pelvis with IVU and cystogram film followed by ascending urethrography in an attempt to make an initial diagnosis. Where a diagnosis could not be made, or complete rupture was suspected, operative exploration was undertaken. The investigative findings, treatment and results are presented.

Patients and Methods

Patients with clinical evidence of injury to the posterior urethra were subjected to immediate IVU, followed by ascending urethrography in the Accident and Emergency Department of the Royal Infirmary. Where the lower urinary tract was shown to be intact (Figs 1 and 2), no further urological investigation was carried out. Those patients whose investigations showed urethral damage were treated as outlined below.

Twenty-eight patients were admitted between 1973 and 1983 with demonstrable posterior urethral injury. There were 27 male patients and 1 female. The age range was 18 to 83 years (average 45). Five patients, including the only female patient, died of multiple injuries shortly after admission. The cause of urethral trauma was road traffic accident in 20, industrial injury in 6 and fall from a height in 2 patients. The soft tissue injuries accompanying the fractured pelvis are shown in the Table.

Radiological Investigation

Intravenous Urogram. A modified IVU was performed consisting of a plain film, a single renal film and a cystogram. Particular attention was paid to the position and shape of the bladder. Twenty-five patients had an IVU immediately on reception; the one female patient died immediately upon reception and two were referred several days after admission. There were therefore 25 IVUs for analysis.

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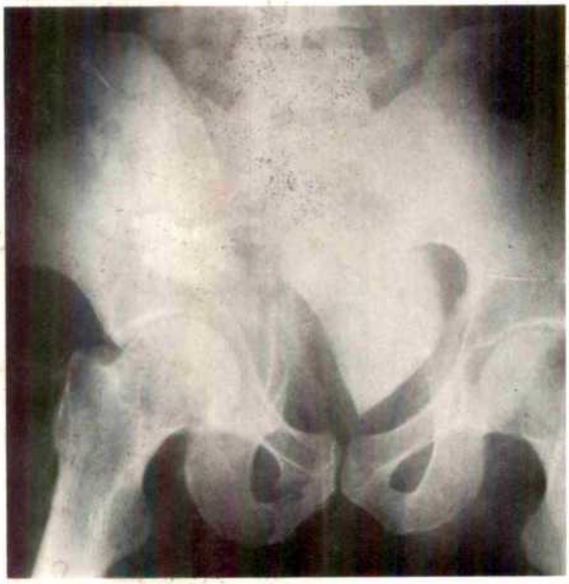

Fig. 1 AP view of cystogram film of IVU showing distortion of bladder.

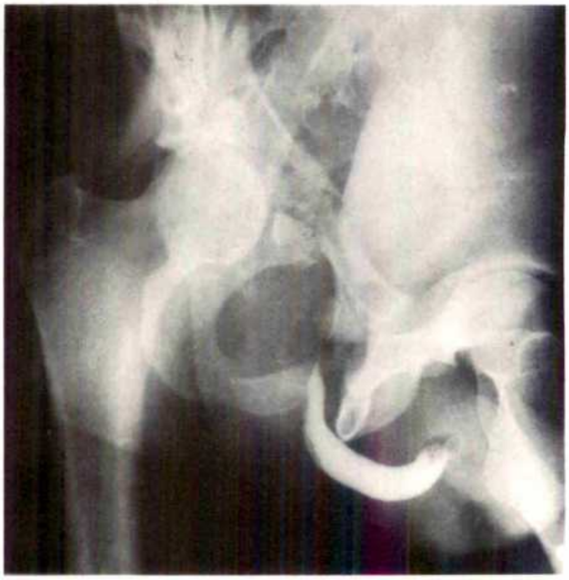

Fig. 2 Oblique ascending urethrogram of Figure 1 showing urethra to be intact.

Table Soft Tissue Injury

Rectal rupture	2
Tear of anal canal	1
Rectal bleeding secondary to rectal carcinoma	1
Burst injury to intestine ± torn mesentery	5
Rupture of liver	1
Rupture of bladder	2
Head and chest injury	4

Displaced Bladder. There were five patients whose cystogram showed the bladder to be high within the pelvis with little or no distortion (Fig. 3).

Twenty patients had a bladder in normal relation to the pubis, either with a normal outline (Fig. 4) or minimal distortion.

Ascending Urethrography. Twenty-seven male patients had ascending urethrography, 25 immediately upon admission and after IVU and two at 5 and 7 days respectively, having been admitted to other units. They were divided into three groups:

Group 1 An obvious injury but with dye entering the posterior urethra, indicating a partial injury (7 patients) (Fig. 5).

Group 2 A tear confined to one side of the posterior urethra (segmental tear) (2 patients) (Fig. 6).

Group 3 Gross extravasation of dye without evidence of onward passage into the posterior urethra, the cystogram being part of the IVU; the degree of injury was unknown (18 patients) (Fig. 7).

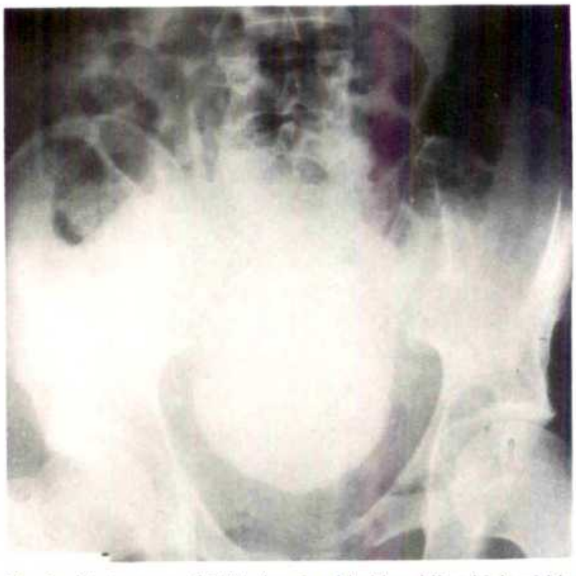

Fig. 3 Cystogram of IVU showing bladder riding high within pelvis.

Pre-operative Diagnosis. An attempt was made to reach a pre-operative diagnosis on the basis of the position of the bladder combined with the urethro-

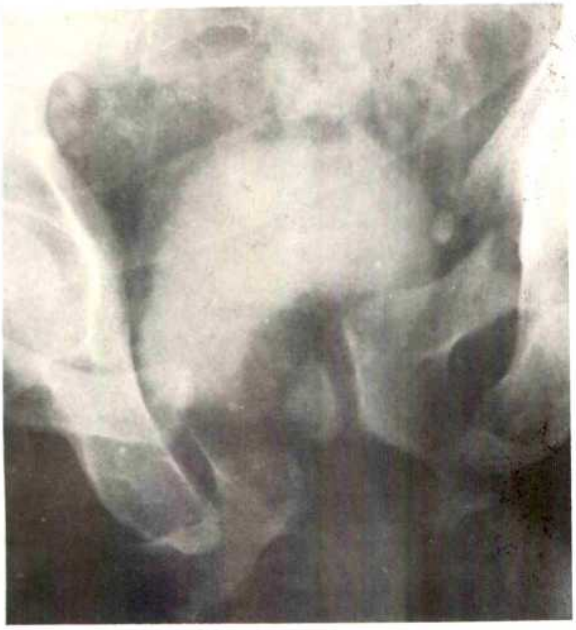

Fig. 4 Cystogram of IVU showing bladder in "normal" position with reference to pubis.

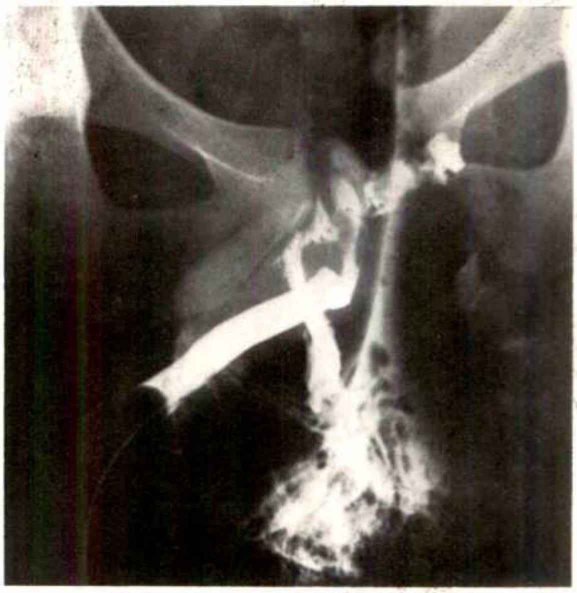

Fig. 6 Ascending urethrogram with dye extravasating from local tear in prostatic urethra.

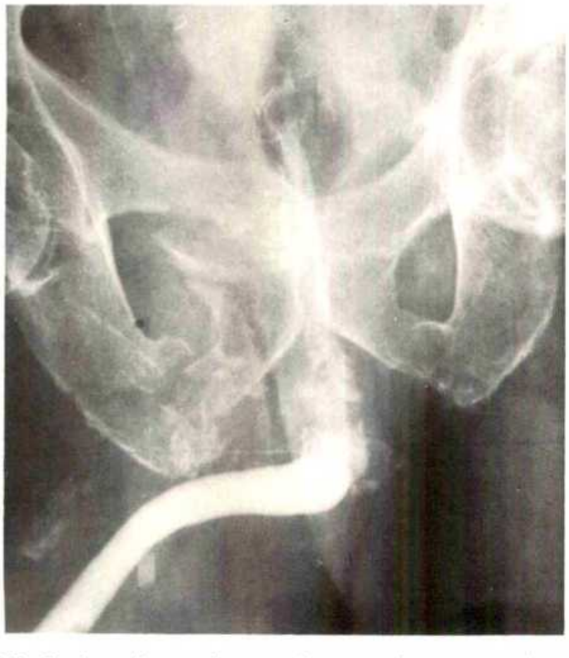

Fig. 5 Ascending urethrogram demonstrating extravasation of dye at level of membrane but with dye entering the posterior urethra.

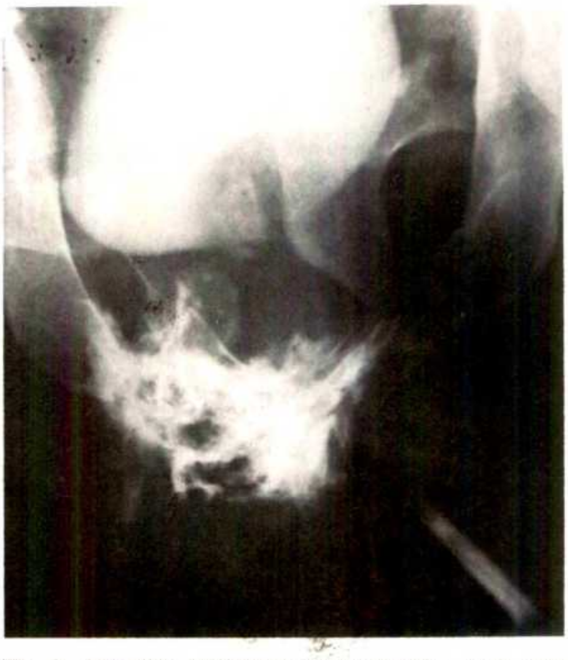

Fig. 7 Ascending urethrogram demonstrating gross extravasation at level of prostato-membranous junction.

gram, bearing in mind the difficulty in interpretation of the X-rays.

Taking the cystogram and ascending urethrogram in conjunction, those with high-riding bladders had urethrography in Group 3; this was felt to indicate either complete or near-complete disruption of the ligamentous support of the prostatomembranous segment and significant disruption and/or separation of the membranous from the prostatic urethra.

Those patients with dye entering the posterior urethra usually had bladders in the normal position with or without distortion and therefore a partial injury.

The largest group, however, were those patients with the bladder in the normal position with gross extravasation on urethrography (Fig. 7); although a major injury was obviously present, it was impossible to say whether this was complete or incomplete.

Management

Patients with proven partial injury were treated by either percutaneous cystostomy or formal cystostomy. Thereafter urethrography was carried out at weekly intervals until voiding commenced or rapid stricturing was apparent; where occlusion occurred, urethroscopy was immediately undertaken with a view to restoration of patency. Those patients with either complete dislocation or suspected near-total rupture were, when their general condition was suitable, subjected to exploration to ascertain the exact nature of the lesion. They were then treated either by cystostomy when partial injury was demonstrated, or realignment when total or sub-total injury was confirmed.

Technique of Realignment

Unless dictated by other injury, a lower abdominal mid-line incision was performed and the retropubic space entered. The prostate was examined with regard to mobility and an attempt was made to assess the degree of ligamentous attachment. Where the prostate appeared to have fixation to the pubis or perineal membrane, then a cystostomy alone was performed. However, if the prostate could be moved without force to one side or another, displaying the membrane, or was obviously free, then realignment was carried out. A 20F Silastic catheter was passed *per urethram* into the pelvis, where it was easily seen; the bladder was opened and inspected and a 22F catheter passed down the proximal urethra and into the pelvis. The urethral catheter was sutured to the bladder catheter and then led into the bladder, thus avoiding tearing, false passage or inverting mucosa at the section line. The urethral catheter balloon was inflated and sufficient traction applied to reduce the displacement. The catheter was then marked by a stitch at the external meatus and sliding traction set up to maintain the mark at the meatus. The amount of traction needed was small. Thereafter the bladder was closed round the suprapubic catheter. The retropubic space was drained and broad spectrum antibiotic cover instituted for 5 days. Where the prostate was totally dislocated it was possible in two patients to carry out direct suture of the membranous to prostatic urethra.

Partial Rupture

Nine patients were diagnosed as having partial urethral injury; two of those had segmental injury. Two patients underwent percutaneous cystostomy because of head and chest injuries and seven had a formal cystostomy.

Laparotomy. Eighteen patients were considered for laparotomy. Two had severe head injuries. The cystogram had shown the bladder to be in the normal position and they were subjected to percutaneous cystostomy alone. Sixteen patients were explored. The five suspected of dislocation of the prostate had this confirmed. Of the 11 other patients, seven were found to have total or near-total rupture with little remaining ligamental support. Twelve patients therefore had primary realignment. Four patients had only minor ligamentous disruption; two were treated by cystostomy and in two it was possible to pass a catheter retrogradely down the urethra and reintroduce the urethral catheter. Both of these patients died of other injuries. Overall, 5 of 28 patients died of multiple injuries. There were therefore 12 patients who had primary realignment and 11 treated by cystostomy who survived. Two of these had segmental avulsion and are considered separately.

Primary Realignment

Twelve patients underwent primary realignment, two by direct suture over a 20F Silastic catheter and 10 by traction over a similar catheter. The urethral catheter was removed at 10 days and urethrography performed. This was repeated at weekly intervals until healing was complete, as shown by cessation of extravasation of dye at the site of injury. The suprapubic catheter was then removed. Two patients (direct suture) healed in less than 2 weeks, three by 2 weeks, four at less than 1

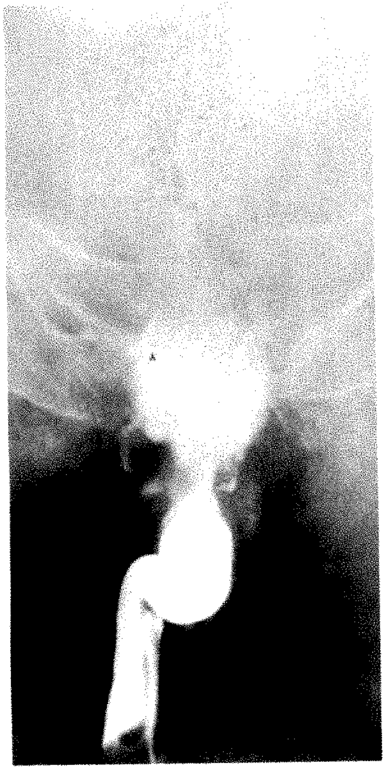

Fig. 8 Gross extravasation at prostatomembranous junction but with dye in the posterior urethra.

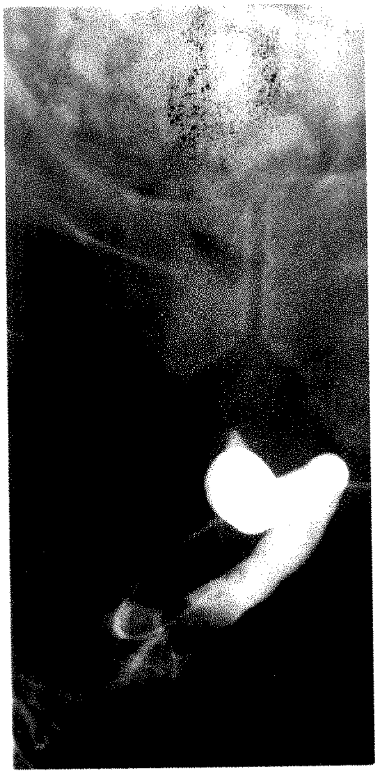

Fig. 9 One week after urethrogram in Figure 8 showing complete occlusion at membrane.

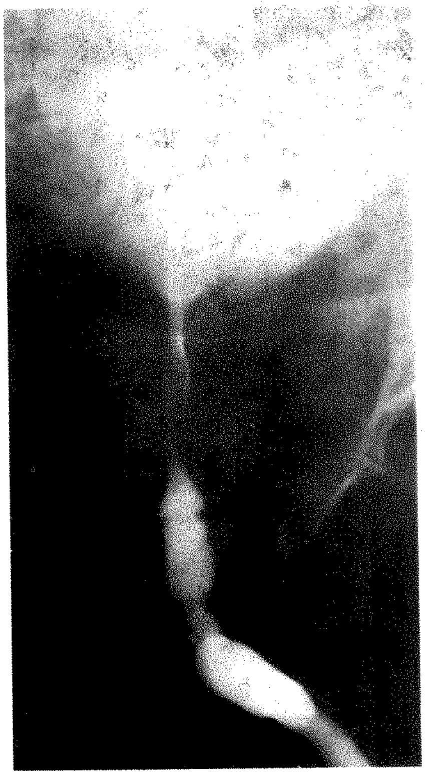

Fig. 10 Urethrogram 12 days after optical urethrotomy.

month, and two took between 6 and 8 weeks after injury before healing was complete. One patient in this group required re-catheterisation at 3 weeks because of continued leakage of dye plus a tendency to rapid stricture.

Long-term Follow-up

The patients underwent a urethroscopy at 1 month. The urethra was calibrated by bougies at 2, 4 and 6 months and thereafter at 6-monthly intervals. The follow-up period ranged from 1 to 10 years (average 4). There has been no tendency to aggressive stricture formation within this group and no patient has symptoms referrable to his stricture.

Incontinence

Two patients in this group demonstrated stress incontinence; both were direct crush injuries. One had impotence and a neurogenic decentralised bladder on cystometry.

Impotence

Two patients are impotent; both have decentralised bladders on cystometry.

Partial Rupture

Of the 11 patients with partial rupture, two had segmental rupture in the face of severe pelvic crush injury. They were referred at 5 and 7 days respectively with retropubic infection and fistulae (Fig. 6). Both required catheter drainage for 9 months and 1 year respectively before healing occurred. They have shown no tendency to stricture. Nine other patients were treated by simple cystostomy alone; two patients voided spontaneously between 7 and 10 days. All others, followed by weekly urethrograms (Figs 8 and 9), went on to complete stricture between 1 and 3 weeks after injury and required surgical intervention to re-establish continuity. Five were managed by urethrotomy endoscopically between 7 and 14 days after injury (Fig. 10) but two required suprapubic and perineal exploration 3 weeks after injury. Urethrotomy involved either cutting blindly into the occluded membrane, where suprapubic exploration was also undertaken; the bulge of the catheter passed from above allowed the proximal urethra to be located. A Silastic urethral catheter was left indwelling for a further 3 weeks and they were then managed as for complete ruptures. The follow-up period ranged from 2 to 9 years (average 3-5).

Impotence. One patient in this group is impotent (segmental damage) and is known to have a decentralised bladder. No patient was incontinent. Initially they all had a greater tendency to rapid stricture than the realignment group but this was controlled by bouginage at 3-weekly intervals for approximately 3 months, when the tendency to stricture settled and they are all again managed with 6-monthly or yearly calibration. No patient is symptomatic regarding the stricture at present.

Discussion

The aims of treatment in posterior urethral injury must be to limit the extent and degree of stricture and if possible to avoid compounding the injury, thus increasing the risk of incontinence and/or impotence. Where wide separation of the prostatic and membranous urethra occurs, then inevitably a long and dense stricture results (Glass *et al.*, 1978) whereas, as has been shown, partial injury results in only a very short stricture. It would therefore seem reasonable to reduce the dislocated prostate and realign a complete rupture of the urethra. Similarly, to realign a partial injury involves either extensive dissection to display the torn urethra or a blind procedure such as "rail-roading", with no knowledge of whether the true urethra has been cannulated or false passages created. The treatment plan outlined above was adopted in 1973 with the proviso that an accurate diagnosis be made in each case. Of 28 patients seen, five died of their injuries at or soon after admission, usually of head or chest trauma. The cystogram film of the intravenous urogram at reception proved invaluable by allowing accurate percutaneous cystostomy to be carried out, so removing the necessity for blind puncture or formal cystostomy. Accurate pre-operative diagnosis was made in 14 of 23 patients on the basis of the IVU and urethrogram. In the 11 patients subjected to exploration, seven were found to have total or sub-total injuries; four had, however, significant remaining ligamentous support. Gross extravasation of dye within the pelvis therefore is not grounds for an absolute diagnosis of complete rupture, providing the bladder neck is in normal relation to the pubis. In this series, where the bladder was high within the pelvis and undistorted at its base and where urography was in Group 3, complete disruption with dislocation was confirmed by exploration. Where total or sub-total rupture was present, then a catheter passed *per urethram* entered the pelvis and was easily located without sharp dissection or forcible manipulation of the prostate. Realignment over a Silastic catheter, by the two-catheter technique, was simple, speedy and atraumatic. The weight of traction was controlled by intra-operative reduction of the prostate and by marking the catheter at the external meatus when this was accomplished. There was no case of retropubic infection in the realignment group and wounds unrelated to colostomies healed rapidly. Once realigned, healing of the urethra occurred between 2 and 8 weeks. One patient showed signs of rapid stricturing and this was controlled by a further 3 weeks' catheterisation. Re-catheterisation in this case was accomplished *per urethram* without difficulty but underlines the need for either visual or radiographic control of healing. Two patients were incontinent and two were impotent (one having both complications) in the total/sub-total disruption group. In view of the lack of manipulation at the time of surgery the initial pelvic injury is the most likely cause of these complications. It is possible that the often prolonged excess traction which used to be applied to the urethra could have contributed to these complications in the past, but unlikely in the form of controlled traction now applied.

The treatment of partial injury by suprapubic cystostomy alone was disappointing in one respect—that only two of nine patients voided spontaneously and the others all went on to complete urethral occlusion. Treatment by endoscopic urethrotomy alone was accomplished in five at between 1 and 2 weeks and whilst stricturing in the immediate post-catheter period seemed more aggressive than following the primary realignment, this was controlled at 3 months. The two patients with a portion of the prostato-membranous urethra avulsed required 9 months and 1 year to heal, possibly due to local sepsis. Once healing had occurred they showed no tendency to stricture at follow-up (4 and 8 years respectively). One of these patients is impotent and has a decentralised bladder on cystometrography. No other patient in the partial injury group was either incontinent or impotent. Long-term stricture formation has not been a problem in that all patients have been carefully followed up by urethral calibration. After 6 months there seemed to be little tendency for rapid stricturing. However, to wait to see if significant stricture occurs, when the natural history suggests that this will do so, simply visits more operative treatment upon the patient. We are therefore unable to give a true stricture rate; suffice it to say that no patient has symptoms referrable to stricture and none has required urethroplasty. They are kept under review at either 6-monthly or yearly intervals and have not found this a burden. The absence of aggressive stricturing may in part be ascribed to the inert material of the Silastic catheter compared with rubber or latex used in the treatment of patients in earlier series.

In conclusion, we have found that primary realignment of total or sub-total posterior urethral rupture is a safe procedure, producing an acceptable result, and that impotence and incontinence seem to be related to the initial injury. Partial injury, if severe, will result in total membranous occlusion which will require excision if left, but may be treated urethroscopically at between 1 and 2 weeks. The treatment of choice, where a definite diagnosis of partial injury is made, is percutaneous cystostomy followed by urethrographic studies weekly and, where occlusion is seen to be occurring, then urethroscopy and urethrotomy (Mitchell, 1968) should be proceeded with immediately. Careful initial diagnosis and management as outlined above have resulted in symptomatic cure of the patient's urethral tear and avoided the necessity for urethroplasty.

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The Authors

J. W. Fowler, FRCS, Consultant Urologist, Royal Infirmary, Edinburgh.
G. Watson, FRCS, Consultant Urologist, Ballochmyle Hospital, Cumnock.
M. F. Smith, TD, FRCS, Consultant Urologist, Law Hospital, Carluke.
J. R. MacFarlane, FRCS, Consultant Urologist, Victoria Hospital, Kirkcaldy.

Requests for reprints to: J. W. Fowler, Department of Urology, Wards 15/16, Royal Infirmary, Edinburgh EH3 9YW.

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The Use of Split-skin Mesh Graft in the Management of Urethral Strictures

H. LIPSKY

Department of Urology, Leoben Hospital, Leoben, Austria

Summary—In the last 3 years 268 patients with urethral strictures have attended this unit. We treat most strictures by urethrotomy and consider an open operation only after two recurrences or in patients whose strictures are considered unsuitable for urethrotomy. Open operations have been performed on 42 patients. Although several types of operation have been used, most comprised an end-to-end anastomosis or Blandy's scrotal flaps.

In the last few years a split-skin mesh graft has been used to replace the posterior urethra and the advantage of this technique is that the new urethra is soft and hairless. We present our experience with this method and our overall results.

In the last decade direct vision urethrotomy has become a generally accepted method of treating urethral strictures. In many patients the stricture recurs within a year and urethrotomy has to be repeated, often many times. This form of treatment resembles the traditional way of treating a stricture by dilatation, the only advantage being that the symptom-free periods are longer (Sachse, 1974; Lipsky and Hubmer, 1977; Johnston *et al.*, 1980; Pain and Collier, 1984).

Although we treat many patients by urethrotomy, our enthusiasm for it has declined. We consider an open operation as the first line of treatment if the patient has a long or multiple stricture and if two urethrotomies have failed. In this unit the number of open operations has increased over the last few years (Fig. 1). We have used several one-stage and two-stage procedures. This report describes a technique of urethroplasty using a split-skin mesh graft described by Schreiter (1984).

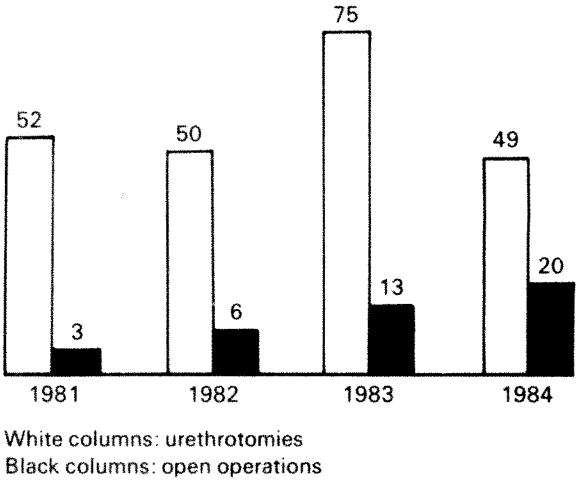

Fig. 1 Treatment of urethral strictures.

Patients and Methods

We have operated on 42 patients over a 4-year period. The cause and site of the strictures are shown in Table 1. Some were situated near the sphincter but none at the site of the external sphincter.

Technique

The graft can be obtained from the inside of either the forearm or the thigh and must be superficial to

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Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

Table 1 Strictures Treated by Operations (n = 42)

Aetiology:	
iatrogenic	23
inflammatory	9
traumatic	10
Localisation:	
anterior	13
posterior	14
multiple or long stricture	15

Table 2 Results of Strictures Managed by Open Operations (n = 42)

		Good and satisfactory	*Recurrence*
Patch	4	1	3
Island flap	1	1	
End-to-end anastomosis	6	2	4
Blandy's scrotal flap	6	5	1
Marsupialisation	4	4	
Mesh graft	21	17	4

the hair follicles. Alternatively, the foreskin can be used and if so the operation starts with a circumcision. The foreskin is pinned out on a cork plate and its subcutaneous tissue carefully removed. The graft is then meshed, using a mesh graft dermatome (Blandy *et al.*, 1968; Berger *et al.*, 1976; Brannam *et al.*, 1976), and put into saline solution.

The patient is placed in the lithotomy position. The urethra is exposed by a longitudinal incision and opened in the usual way at the distal healthy site (Fig. 2). The stricture is cut over a metal probe to the healthy proximal part of the urethra. The opened corpus spongiosum is sewn with a running suture in order to control the bleeding. The mesh graft is divided in the middle, placed on both sides of the diseased part of the urethra and fixed in place with single stitches of Dexon (Fig. 3). A catheter is inserted into the bladder (Fig. 4). The skin is stitched to the margins of the mesh graft with silk. Gauze and pads are put on the transplant and tied in with the long ends of the skin stitches (Fig. 5).

Post-operative treatment

The dressing is removed after 5 days and the wound cleaned and dressed daily. The catheter is removed after 1 week and the patient discharged 10 days after operation. Weekly dilatations ensure that no adhesions occur. The patient is told to bathe daily.

The urethra is reconstructed 3 to 6 months after the first stage. The new urethra is formed over a 24 F catheter and closed with running stitches (Fig. 6). A catheter is left *in situ* for 10 days.

Results (Table 2)

The follow-up period was from 9 months to 2 years. The primary results were excellent in all but four patients. In three cases the recurrence was due to insufficient splitting of the diseased urethra and although most of the graft healed satisfactorily, a further urethral stricture developed. In one patient, who was lost to follow-up, adhesions occurred within the graft and a further operation was necessary. The second mesh graft cured all patients. Four patients refused a second stage and void in the sitting position. All had already undergone several urethrotomies and/or urethroplasties. All 21 patients void well and are pleased with the results. Urethrography showed urethras of normal width except in the case of three patients whose new urethras are irregular and have pouches because the second stage was not done correctly.

Discussion

Open operations do not produce the best results in the hands of all surgeons and direct vision urethrotomy is not the ultimate solution for all stricture problems. Experience with urethral strictures shows that there will always be a place for open surgery.

There are several operative techniques for the management of urethral strictures. They are usually two-stage procedures, where a scrotal skin inlay is placed at the site of the stricture (Blandy *et al.*, 1968; Turner-Warwick, 1968). One of the problems with this technique is that hair in the inlay may lead to stone formation, especially if the new urethra is too wide, and even depilation cannot always prevent this. Resection of the stricture with end-to-end anastomosis cannot be used for all strictures and the results of one-stage full thickness skin grafts are controversial (Devine *et al.*, 1963; Berger *et al.*, 1976; Brannam *et al.*, 1976). A two-stage procedure enables the diseased urethra to drain and heal properly and the surgeon can always be sure that the operation is successful because the second stage is usually a simple procedure.

The method described is a step forward in urethral surgery and has the advantage that soft and hairless tissue of any required length is available. The graft can be put on inflamed and scarred tissue and the mesh guarantees free drainage of all secretions. Epithelialisation of the graft occurs very quickly. With this technique it is possible to deal with strictures of the whole length of the urethra, though we have not used it in strictures above the sphincter.

Schreiter (1984) reported excellent results in 64 patients and after 7 years none showed restricture or shrinkage of the graft. Our results confirm his work. Although we have used this technique for only 2 years we can recommend it, especially for patients who have already undergone surgery.

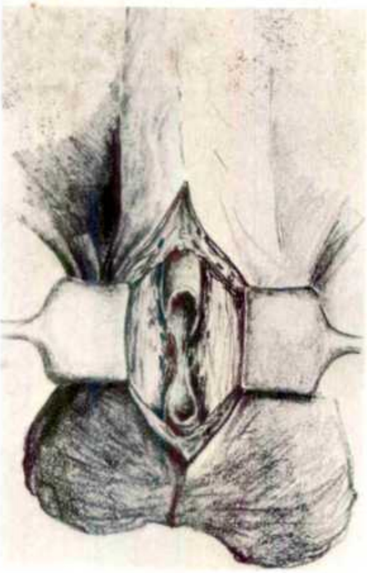

Fig. 2

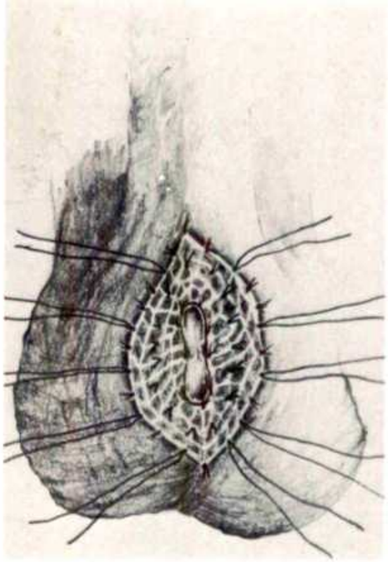

Fig. 3

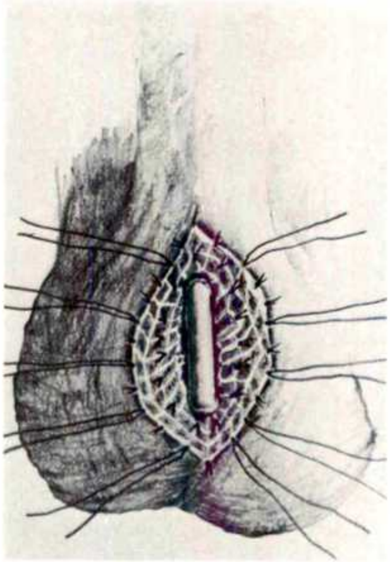

Fig. 4

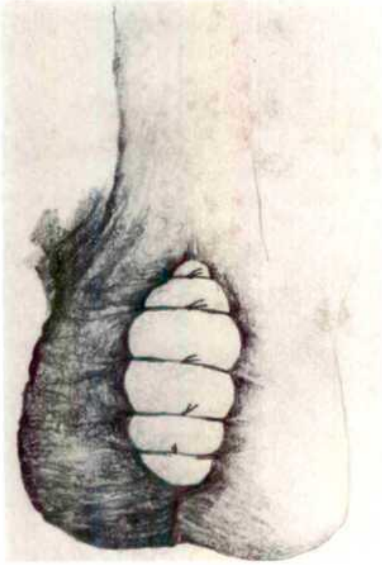

Fig. 5

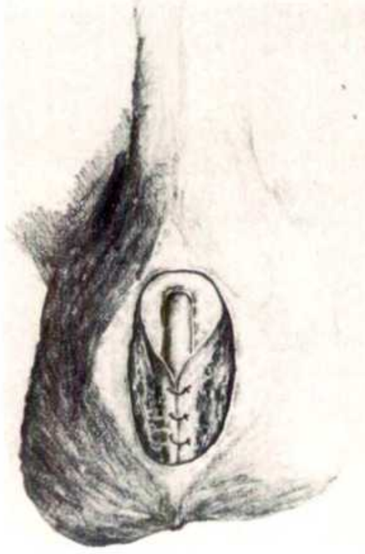

Fig. 6

Fig. 2 The stricture is exposed and split on both sides into the healthy part of the urethra.

Fig. 3 The mesh graft is incised and put on both sides of the stricture.

Fig. 4 An indwelling catheter is in place.

Fig. 5 The wound dressing is tied with the ends of the skin stitches.

Fig. 6 The second-stage graft is circumcised and a tube formed over a catheter.

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The Author

H. Lipsky, Urologist, Urologische Abteilung, Landeskrankenhaus Leoben 8700, Vordernbergerstrasse 42, Leoben, Austria.

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Indications for Ultrasound in the Evaluation of the Pathological Scrotum

R. F. SCOTT, A. P. BAYLISS, J. F. CALDER and W. H. H. GARVIE

Departments of Radiology and Urology, Aberdeen Royal Infirmary, Aberdeen

Summary—Scrotal ultrasound scans carried out on 156 patients were reviewed in a retrospective study and the sonographic findings and indications evaluated. Ultrasound was able accurately to distinguish the normal from the pathological scrotum. Extratesticular lesions were readily differentiated from testicular lesions. Abnormal testicular echo patterns were usually associated with tumours, but orchitis, granulomas and haematomas were found to have a similar appearance. Occult testicular tumours could readily be identified. Ultrasound was also useful in excluding underlying pathology in hydroceles, in the diagnosis and follow-up of epididymitis and other epididymal lesions and in the assessment of underlying testicular damage in traumatic haematoceles. Ultrasound may also be useful in post-orchiectomy follow-up examinations to exclude tumour in the contralateral testis.

Ultrasound is useful in the demonstration of intrascrotal pathology which is often of great concern to both the patient and his doctor. The indications for ultrasound and its effectiveness in both diagnosis and subsequent management have not been clearly defined. This study reviews the sonographic findings of scrotal scans carried out on 156 patients in this department over a 14-month period and discusses the indications and therapeutic implications. The patients were referred for a wide variety of complaints. These included signs and symptoms directly related to the testis or scrotal contents and included pain, swelling, vague discomfort and palpable masses. Patients with unexplained gynaecomastia were also referred for testicular scans to exclude an occult neoplasm.

Patients and Methods

The scrotal contents of 156 patients were scanned with commercially available real time sector scanners using 5 MHz and 10 MHz transducers. The patients were scanned by direct contact using acoustic coupling gel. Longitudinal, transverse and oblique scans were carried out and prints recorded on heat sensitive paper using a line recorder.

Results

Of the 156 patients who underwent scrotal ultrasound scans, 76 were found to have completely normal scans. These patients were discharged without further follow-up. No false negative scans were recorded. The patients who had positive scans could be divided into two broad groups: those in which the sonographic abnormality was extratesticular and those where the abnormality involved the testicle itself. Testicular lesions could be readily differentiated from extratesticular lesions. A summary of the findings is presented in the Table.

Extratesticular Lesions

Simple hydroceles (Fig. 1) were readily identifiable and abnormalities of the underlying testis and epididymis could be excluded. Cystic lesions of the epididymis (Fig. 2) presented as small, well defined

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Table Summary of Ultrasound Findings and Diagnosis

Ultrasonic findings	*Ultrasonic diagnosis*	*No.*	*Final diagnosis*	*No.*
Normal		76		76
Extratesticular				
Cystic	Simple hydrocele	28	Simple hydrocele	28
	Epididymal cyst/spermatocele	9	Epididymal cyst/spermatocele	9
	Haematoma	1	Haematoma	1
Solid	Epididymitis	23	Epididymitis	23
	Indeterminate mass	2	Fibrous epididymitis	1
			Adenoma of epididymis	1
Testicular	Indeterminate mass	22	Seminoma	11
			Teratoma	6
			Interstitial cell tumour	1
			Epididymo-orchitis	3
			Granulomatous orchitis	1
			Granuloma	1
			Haematoma	1

echo-free regions usually in the head of the epididymis. These represented either simple epididymal cysts or spermatoceles. No differentiation can be made on sonographic grounds between spermatoceles and epididymal cysts (Rifkin *et al.*, 1983). The management of these lesions was essentially non-operative with careful surgical follow-up.

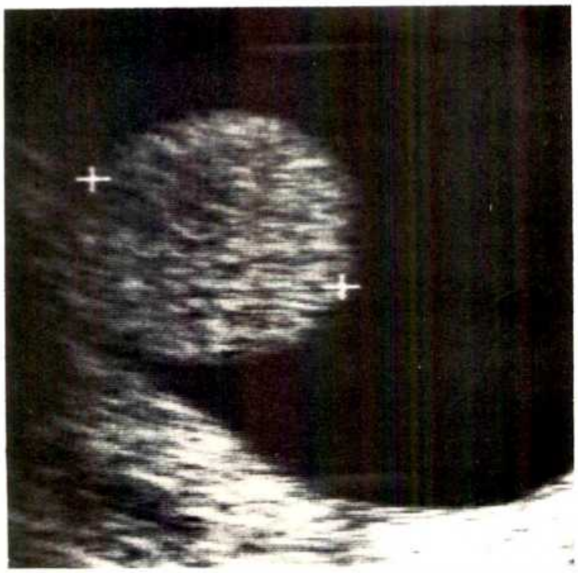

Fig. 1 Large simple hydrocele. Normal testis (between crosses) surrounded by a large echo-free fluid collection.

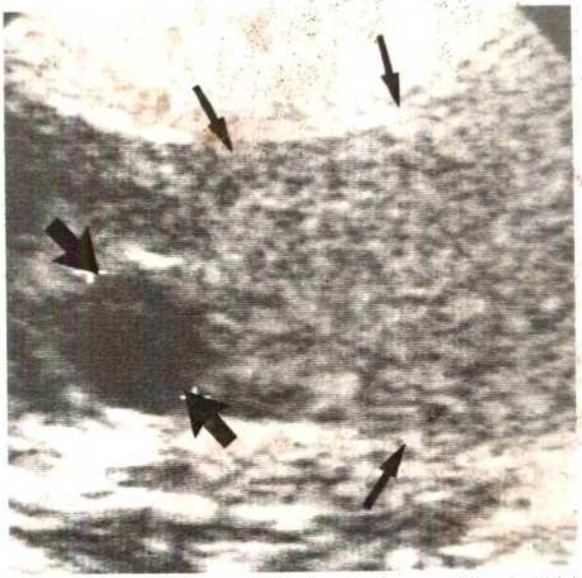

Fig. 2 Small simple cyst in the head of the epididymis (thick arrows). Normal testis (thin arrows).

Epididymitis was relatively common, presenting with a sonographically enlarged epididymis together with decreased echogenicity (Fig. 3). A reactive hydrocele was often present. Some diagnostic difficulty was encountered when the epididymis was shown to be both enlarged and echo-dense. Differentiation between chronic inflammation and tumour of the epididymis was not possible. A

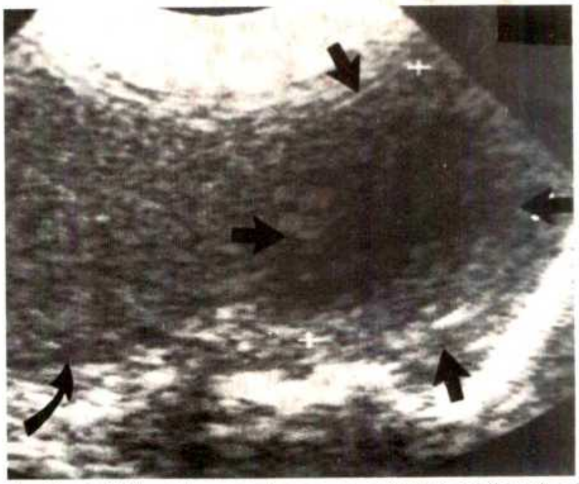

Fig. 3 Epididymitis presenting as an enlarged epididymis of reduced echogenicity (straight arrows). The testis (curved arrows) is normal.

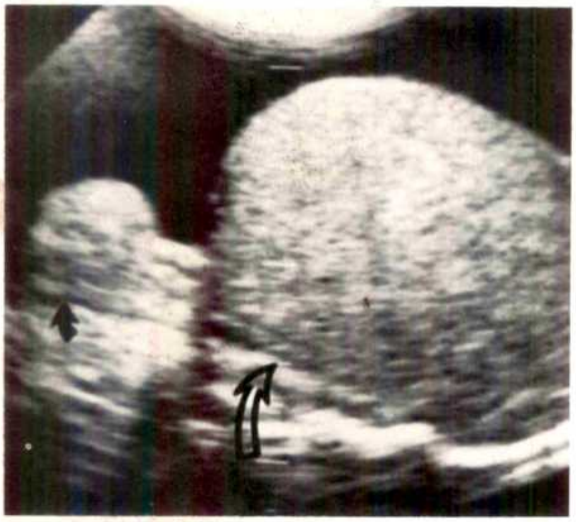

Fig. 4 Enlarged echo-dense epididymis (solid arrow). Normal testis (open arrow). A large reactive hydrocele is present.

patient presenting with an enlarged epididymis of increased echogenicity and moderate reactive hydrocele (Fig. 4) was found on resection to have fibrous epididymitis. A similar sonographic appearance was found in a patient with an adenoma of the epididymis.

A haematocele showed a large intrascrotal fluid collection with some organisation and loculation (Fig. 5). The underlying testis and epididymis were normal.

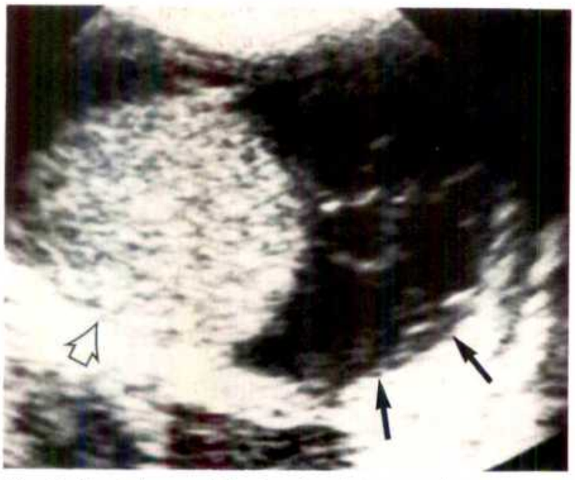

Fig. 5 Scrotal scan following local trauma demonstrates a large loculated haematocele (open arrow) and a normal underlying testis (solid arrows).

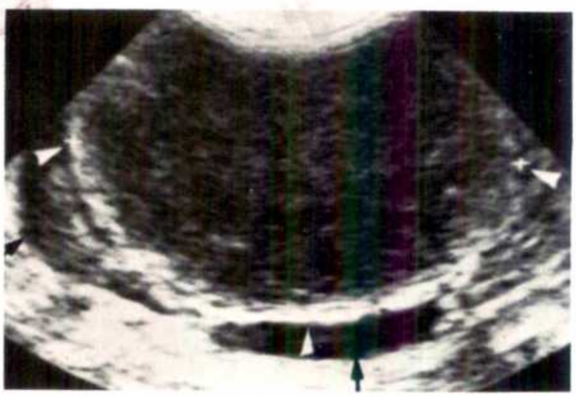

Fig. 6 A sonographically enlarged testis of generalised reduced echogenicity (arrow heads) was on resection proven to be a seminoma. A small hydrocele is present (arrows).

Testicular Lesions

Most testicular lesions presented as areas of decreased echogenicity relative to the normal testicular tissue. There were no specific sonographic features which could be used to differentiate testicular tumour (Fig. 6) from other testicular lesions such as haematoma (Fig. 7), granuloma (Fig. 8) and orchitis. Although most tumours presented with decreased echogenicity, three cases of teratoma (50%) presented with areas of mixed echogenicity (Fig. 9).

One case of orchitis, however, was also found to have a similar appearance of mixed echogenicity.

Two patients referred for testicular scans during the investigation of unexplained gynaecomastia were found to have occult testicular neoplasms (Hendry *et al.*, 1984). All patients who had sonographically demonstrable testicular lesions underwent surgical exploration.

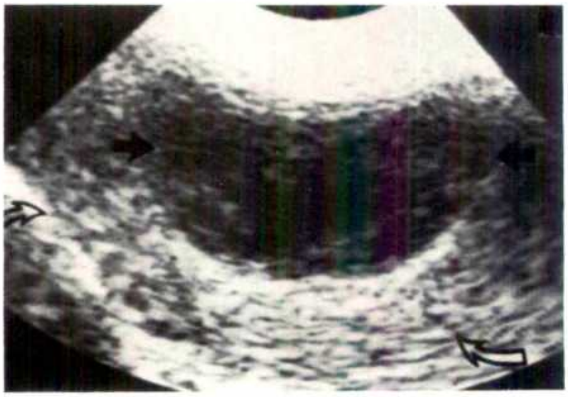

Fig. 7 An intratesticular haematoma presenting as an area of decreased echogenicity (solid arrows) within normal testicular tissue (open curved arrows).

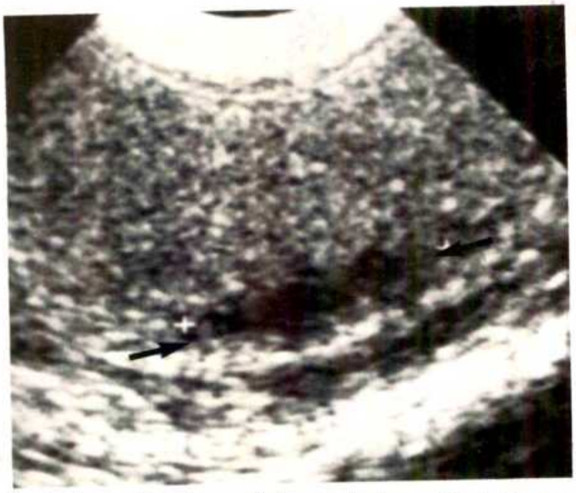

Fig. 8 A small focal area of decreased echogenicity in the posterior aspect of a testis (arrows) was histologically shown to be a granuloma, possibly due to tuberculosis.

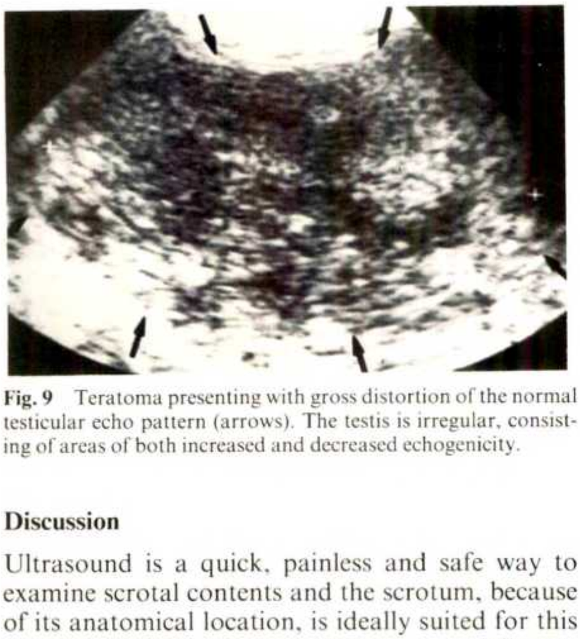

Fig. 9 Teratoma presenting with gross distortion of the normal testicular echo pattern (arrows). The testis is irregular, consisting of areas of both increased and decreased echogenicity.

Discussion

Ultrasound is a quick, painless and safe way to examine scrotal contents and the scrotum, because of its anatomical location, is ideally suited for this purpose. Many intrascrotal lesions, especially testicular ones, are readily demonstrable by ultrasound but are of an indeterminate nature with non-specific sonographic features which are not pathognomonic. There is no accurate way of using sonographic criteria to distinguish benign from malignant testicular lesions. Orchitis, granulomas and haematomas may all present with focal or diffuse areas of decreased echogenicity and are thus sonographically indistinguishable from tumour. Because of the inability of ultrasound to differentiate between various forms of testicular pathology, all echo changes should be regarded as representing potential malignancy unless there is strong clinical evidence to the contrary.

Ultrasound in our experience and in the experience of others (Miskin *et al.*, 1977; Leopold *et al.*, 1979; Ritchie *et al.*, 1982) is accurate in the differentiation of testicular from non-testicular lesions. Cystic lesions are readily distinguishable from solid lesions (Gottesman *et al.*, 1977; Orr and Skolnick, 1980). Hydroceles and more complex fluid collections are easily identified (Ritchie *et al.*, 1982), as are epididymal cysts, spermatoceles and varicoceles (Rifkin *et al.*, 1983).

In patients presenting with a hydrocele of uncertain aetiology and in which the underlying structures cannot be freely palpated, ultrasound provides a useful and accurate means of excluding underlying pathology. The changes which occur in epididymitis, namely enlargement of the epididymis together with decreased echogenicity, are pathognomonic (Rifkin *et al.*, 1983). This is important, since testicular tumours are frequently misdiagnosed initially as epididymitis (Smith, 1969). Ultrasound is therefore a useful adjunct in the diagnosis of epididymitis and the exclusion of testicular tumour. The clinical progress of epididymitis can be followed once the appropriate therapy has been instituted. The size and echogenicity of the epididymis in most cases gradually returns to normal (Rifkin *et al.*, 1983). Chronic inflammation presenting as an enlarged epididymis of increased echogenicity is not distinguishable from a tumour of the epididymis. Resection is usually necessary.

Ultrasound has also been shown to be useful in the diagnosis of malignant tumours in the palpably normal testis (Bockrath *et al.*, 1983; Emory *et al.*, 1984; Hendry *et al.*, 1984). Patients presenting with unexplained gynaecomastia or an abdominal mass of unknown origin should have a testicular scan to exclude an occult testicular neoplasm. There is a higher incidence of tumour in the contralateral testis in a patient who has been operated on for tumour of the testis (Forsberg and Olsson, 1983) and follow-up scans of the remaining testis should be done in these patients to exclude tumour. In a patient with a traumatic haematocele, ultrasound is able to ascertain whether or not the underlying testis is intact. Appropriate surgical management can then be instituted. Finally, the importance of the normal scan should not be forgotten, as it provides great relief from anxiety for both patient and doctor.

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The Authors

R. F. Scott, MB,BCh, DMRD, Senior Registrar, Department of Radiology.

A. P. Bayliss, DMRD, FRCR, Consultant Radiologist.

J. F. Calder, DMRD, FRCR, Consultant Radiologist.

W. H. H. Garvie, FRCS, FRCSE, Consultant Urological Surgeon.

Requests for reprints to: R. F. Scott, Department of Diagnostic Radiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZB.

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Scanning Electron Microscopy of Adenomatoid Tumours

J. A. MORRIS, K. OATES and W. G. STAFF

Department of Pathology, Lancaster Moor Hospital; Department of Biological Sciences, University of Lancaster; Department of Urology, Royal Infirmary, Lancaster

Summary—Four adenomatoid tumours of the epididymis were embedded in paraffin wax, sectioned and the sectioned surfaces examined by scanning electron microscopy using the secondary electron mode. The solid faces of the sectioned neoplasms were damaged by the preparative technique but the depressed luminal surfaces of the tubules were well preserved and yielded useful information. Large areas of luminal surface were examined and the presence and distribution of microvilli were noted. In addition, there was a more complex cell surface pattern of intersecting cord-like elevations. Desquamating cells were seen within the tubules and the cytoplasmic bridges noted by light microscopy were shown to be thin cytoplasmic partitions. These findings are consistent with the mesothelial theory of histogenesis.

Scanning electron microscopy can provide useful information about the internal structure of neoplasms even with simple preparative techniques.

Adenomatoid tumours, although rare, have aroused considerable interest because of their uncertain histogenesis. A series of studies using transmission electron microscopy (TEM) (Akhtar *et al.*, 1967; Marcus and Lynn, 1970; Mackay *et al.*, 1971; Ferenczy *et al.*, 1972; Salazar *et al.*, 1972; Taxy *et al.*, 1974) provided strong support for a mesothelial cell origin, although the fact that these tumours are almost exclusively located in genital organs has never been adequately explained.

Scanning electron microscopy (SEM) has certain advantages over TEM. The preparative techniques are simple, large areas of tissue can be examined, a three-dimensional view is obtained, and multiple modes of analysis are available. This technique has been used to study natural body surfaces but there are few studies of the internal structure of neoplasms (Buss and Hollweg, 1980; Carr *et al.*, 1980).

We report the first SEM study of adenomatoid tumours, the aim of which was to extend our understanding of the structure of these neoplasms and to make some assessment of the place of SEM in the analysis of solid tissue.

Methods

The four adenomatoid tumours of the epididymis (obtained from patients aged between 46 and 70 years) had been embedded in paraffin wax; they were retrieved from the files and 4 μ sections were cut and stained by haematoxylin and eosin. The paraffin wax was subsequently dissolved in xylene and the tissue blocks were taken through absolute alcohol and ascending concentrations of amyl acetate in alcohol to absolute amyl acetate. They were then critically point dried using liquid carbon dioxide. The surfaces of the blocks which had been sectioned were sputter coated with gold and examined using the secondary electron mode in a JEOL JSM 50A SEM and a JEOL TEMSCAN.

Results

The tumours were macroscopically solid discrete neoplasms from 0.8 to 1.3 cm in diameter. Exami-

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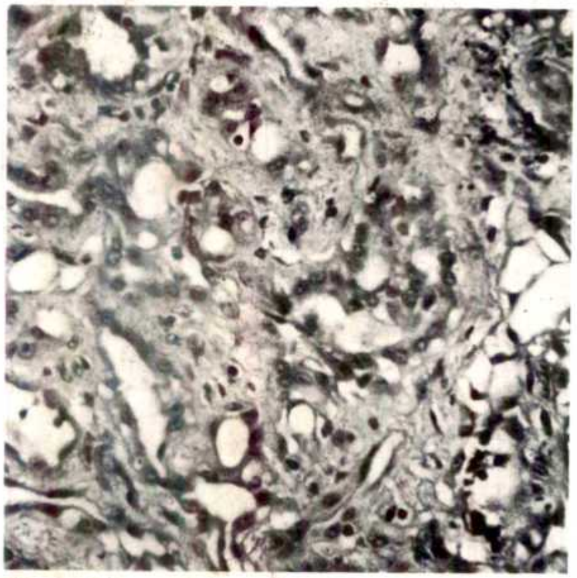

Fig. 1 Adenomatoid tumour. Tubules of varying size in a fibrous stroma. Cytoplasmic bridges cross some of the lumina. (H and E × 250).

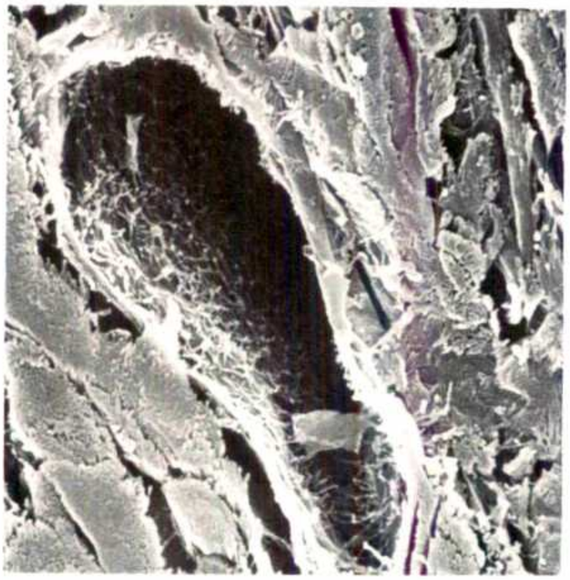

Fig. 2 A tubule in a solid stroma. The solid face shows sectioning artefact but the depressed tubular luminal surface is undamaged. (× 2500).

nation by light microscopy revealed features typical of adenomatoid tumours (Fig. 1). They contained tubules of varying size in a fibromuscular stroma. The tubules were lined by both flattened and plump cells, many of which appeared to be vacuolated. Thin bridges of cytoplasm traversed many of the tubular lumina.

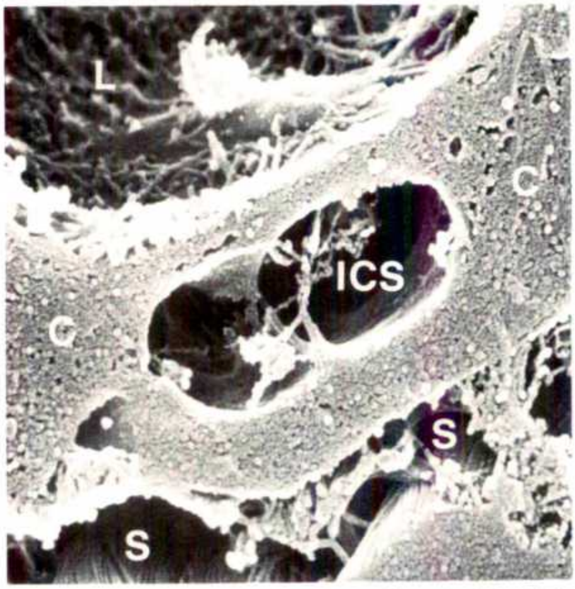

Fig. 3 A tubular lumen (L), the sectioned face of tubular lining cells (C), a prominent intercellular space (ICS) and fissured stroma (S) containing parallel bundles of collagen. (× 10,000).

There was good correlation between the light microscope and SEM images. Low power views showed tubules in a solid stroma (Fig. 2). There was damage to and fissuring of the solid face but the depressed tubular luminal surfaces had not been damaged in sectioning and appeared to be well preserved. There was no discernible cytoplasmic detail on the sectioned face of the tubular or stromal cells and there was a considerable amount of cellular debris on the solid face which made interpretation difficult. In favourable sections, however, where the cut was clean, intercellular spaces between the tubular cells were seen (Fig. 3). The cell membranes around these spaces were often smooth but occasionally had microvillous projections. The fissured stroma revealed parallel bundles of fibres which we assumed to be collagen. The undamaged luminal surfaces showed a complex pattern (Fig. 4). There were abundant microvilli at all angles of inclination, some appearing to lie flat on the surface. In addition there were branching and intersecting cord-like elevations of the cell surface from which the microvilli appeared to arise (Fig. 6b). The density of microvilli varied over the luminal surfaces and in all cases there were some smooth areas, devoid of microvilli and cords, within otherwise typical tubules (Fig. 5). There

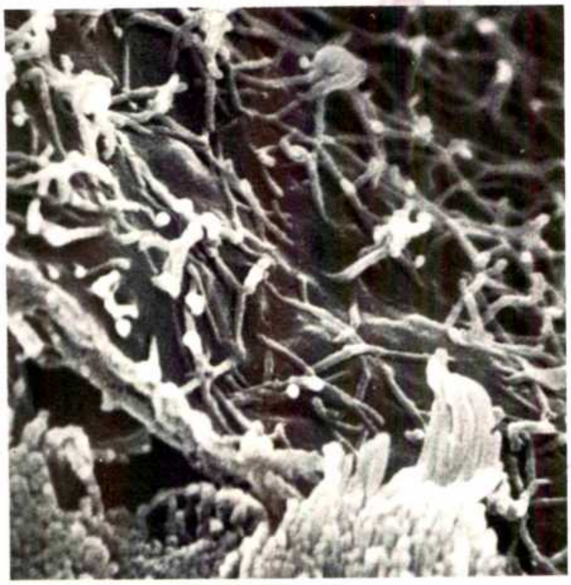

Fig. 4 Tubular luminal surface showing microvilli arising from intersecting cord-like surface elevations. (× 14,000).

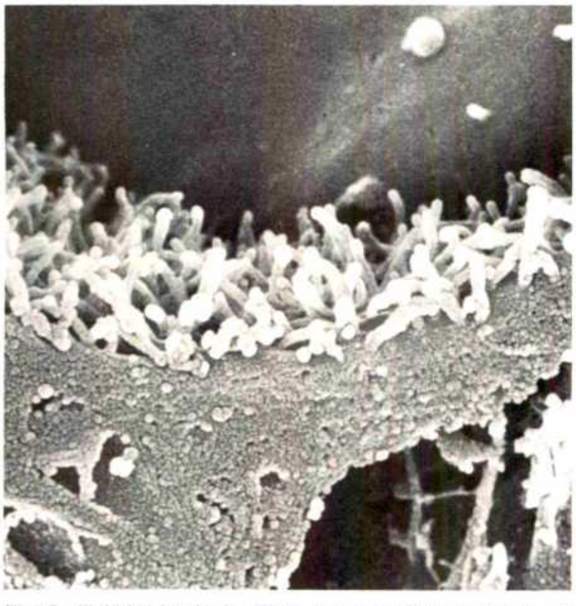

Fig. 5 Tubular luminal surface, part of which is smooth and part of which contains abundant microvilli. (× 14,000).

were cells in the tubular lumina which appeared to be desquamating (Fig. 6). They had a relatively smooth luminal surface, but the lateral and undersides had elongated cytoplasmic processes similar in width to microvilli. The processes ran into and merged with the corded and microvillous processes of adjacent cells. Thin cytoplasmic bridges, which are a characteristic feature of adenomatoid tumours when viewed by light microscopy, were easily seen by SEM (Fig. 7). These structures were viewed at varying degrees of tilt and shown to be thin cytoplasmic partitions.

Discussion

Adenomatoid tumours are rare neoplasms which are almost exclusively located in the genital organs. Initial studies using light microscopy led to various theories of histogenesis, although most workers favoured the idea that they arise from mesothelial cells (Evans, 1943; Golden and Ash, 1945; Jackson, 1958; Hanrahan, 1963; Youngs and Taylor, 1967; Broth *et al.*, 1968; Craig and Hart, 1979). Immunohistological studies using markers for endothelial and mesothelial cells have produced somewhat contradictory results. Bell and Flotte (1982) found Factor VIII antigen in the tumour cells of three out of eight adenomatoid tumours and suggested that some of these neoplasms were derived from endothelial cells. However, Said *et al.* (1982) studied seven adenomatoid tumours and found that whilst they all contained keratin, none of them contained Factor VIII antigen. A series of studies using TEM (Akhtar *et al.*, 1967; Marcus and Lynn, 1970; Mackay *et al.*, 1971; Ferenczy *et al.*, 1972; Salazar *et al.*, 1972; Taxy *et al.*, 1974; Davy and Chik-Kwun, 1981) produced, with one exception (Davy and Chik-Kwun, 1981), strong evidence in support of the mesothelial theory of histogenesis. The tumour cells have surface microvilli, 10 nm cytoplasmic filaments, intercellular junctions and intercellular spaces. These are all features that are seen in other mesothelial cell tumours. Davy and Chik-Kwun (1981), however, examined three cases by TEM and noted evidence of endothelial cell differentiation in one case.

TEM has made important contributions to the study of adenomatoid tumours but the technique is not without limitations. In particular, only minute areas of tissue can be examined and the cells studied may not be representative. SEM is a technique which is relatively untested in the analysis of solid tissue biopsies (Buss and Hollweg, 1980; Carr *et al.*, 1980) but it does have certain advantages over TEM. Much larger areas of tissue can be examined, the preparative techniques are simpler, a three-dimensional image is obtained and this can be enhanced by viewing the specimen at varying degrees of tilt. Furthermore, multiple modes of analysis are now available including the secondary

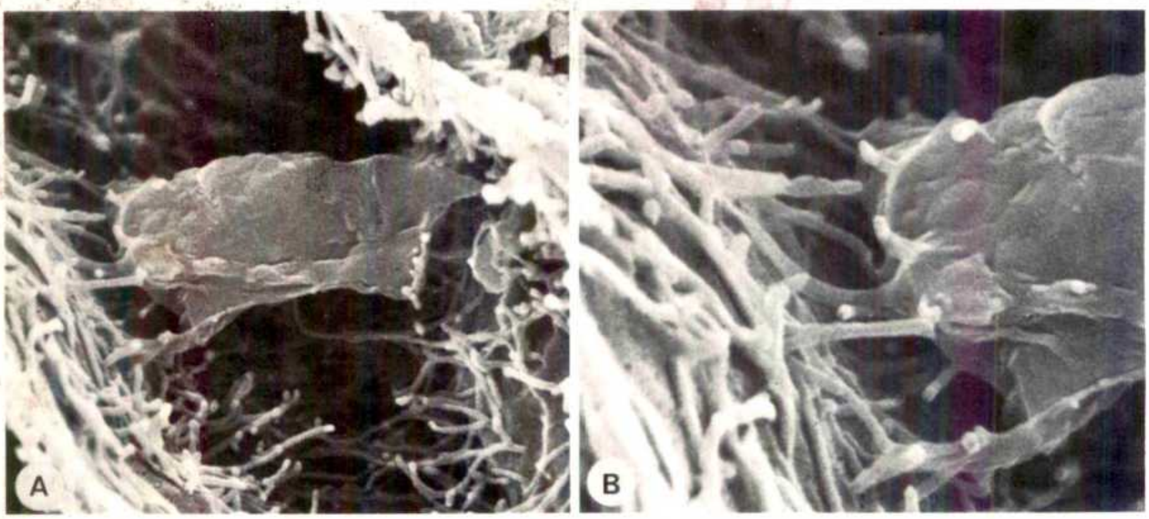

Fig. 6 A tubular lumen containing a cell which appears to be desquamating. The surface of the cell is smooth but the lateral and undersurfaces have elongated cell processes which are similar in width to microvilli. The processes run into and merge with the corded microvillous pattern of the adjacent cells. (A × 14,000; B × 27,500).

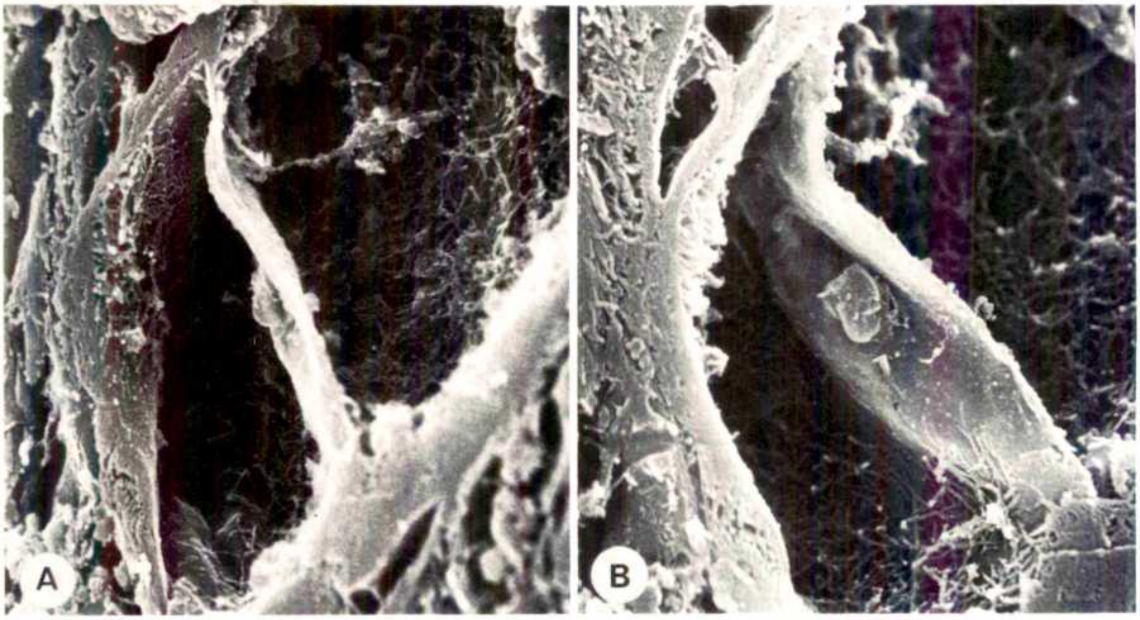

Fig. 7 (A) A tubular lumen crossed by a thin cytoplasmic bridge. (× 4250). (B) The same tubule photographed after tilting the stage, showing that the cytoplasmic bridge is a thin cytoplasmic partition. (× 5500).

electron mode, the backscattered mode, X-ray microanalysis and cathode illuminescence. SEM has been used to study natural body surfaces, but the sectioning or fracturing techniques used to prepare solid tissue for SEM introduce artefact and this has inhibited its use in examining the internal structure of neoplasms. However, we believe that SEM will not make a major impact in routine diagnostic histopathology unless it can be shown to be of value in the examination of solid tissue biopsies. This study, therefore, was designed with a dual aim: to attempt to further our understanding of the structure of adenomatoid tumours and to make some assessment of the place of SEM in the analysis of these lesions.

There was good correlation between the light microscope image and the low power SEM image. Unfortunately the surface of the solid stroma was damaged in sectioning and this limited the information available. However, the luminal surfaces of the tubules were not damaged in sectioning and appeared to be well preserved. In fact large areas of luminal surface were examined and numerous long thin microvilli were noted in all of the tumours. The microvilli were similar in appearance to those described by Dionne and Wang (1977) in mesothelioma of the lung, and therefore this study provides further support for the mesothelial theory of histogenesis. However, a more complex cell surface pattern of intersecting surface cords was also noted and this has not previously been described. The three-dimensional image produced by SEM was of particular value in the study of desquamating luminal cells and thin cytoplasmic partitions.

The presence of microvilli in all of the tumours argues against an endothelial cell derivation, but in all cases some tubules lacked microvilli over part of their surface and it is easy to see how erroneous conclusions could be drawn in TEM studies if the small sections obtained inadvertently contained these bare areas. The ability to study large areas of tissue by electron microscopy is a distinct advantage offered by SEM.

This study has shown that useful information can be obtained by studying the internal structure of neoplasms by SEM using simple preparative techniques. However, only the tubular luminal surfaces were free of sectioning artefact and different preparative techniques will be needed for neoplasms without internal cavities.

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The Authors

J. A. Morris, MRCPath, Consultant Pathologist, Lancaster Moor Hospital.

K. Oates, PhD, Scientific Officer, Department of Biological Sciences, University of Lancaster.

W. G. Staff, MD, FRCS, Consultant Urologist, Royal Lancaster Infirmary.

Requests for reprints to: J. A. Morris, Department of Pathology, Lancaster Moor Hospital, Lancaster LA1 3JR.

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Is a Male Infertility Clinic of Any Use?

T. B. HARGREAVE, B. McGOWAN, JENNIFER HARVEY, MARY McPARLAND and R. A. ELTON

University Department of Surgery/Urology, Western General Hospital, and Medical Computing and Statistics Unit, University Medical School, Edinburgh

Summary—Two methods of statistical analysis were used to evaluate the results from an infertility clinic (the couple-months method and Cox regression analysis). The results were in general agreement and validated the couple-months method. The total trying time, sperm motility, sperm density and results of the wife's investigation were all shown to be highly significant prognostic factors. The age of either husband or wife, semen volume, sperm morphology, size of the testes, presence of a varicocele, serum LH and serum testosterone all failed to give significant additional prognostic information. High serum FSH and testis asymmetry both gave weak additional prognostic information.

The benefit of attendance at the infertility clinic was evaluated in two ways: firstly by testing whether the event of clinic attendance altered prognosis and secondly by examining the results of a broad range of treatments. The results showed that attendance at the clinic with subsequent treatment did not improve the chance of fertility. The main benefit from clinic attendance was that the couple could be given an accurate prognosis and supportive counselling.

The interpretation of the results of treatment for male infertility is difficult for a number of reasons. Firstly, treatment is given to the husband but the desired result is pregnancy in the spouse. This means that both male and female factors have to be considered when evaluating the results of male treatment and this creates considerable organisational problems with records and makes many variables for analysis. In order to avoid the complexities of multivariate analysis, many reports of treatment for male infertility have relied on changes in sperm measurement. The problem with this approach is that sperm measurements are variable (Tjoa *et al.*, 1982), inaccurate (Jequier and Ukombe, 1983) and there is no absolute correlation with pregnancy (Hargreave and Elton, 1983). The advent of computer facilities makes record keeping and multivariate analysis a practical proposition. In this study we have tried to define prognostic factors for male fertility and to evaluate both the benefit from clinic attendance and the results of a broad range of treatments.

Patients

One thousand three hundred and twenty-seven couples were seen at our infertility clinic between 1978 and 1983 and 993 have follow-up information. History taking from both partners was by interview and questionnaire (Hargreave, 1983) and in addition all men were examined. Testicular volume was estimated with a wooden bead orchiometer (Pryor, 1983). Semen analysis was by standard techniques (WHO, 1980). Sperm motility was taken to be the sum of WHO grade 3 and grade 2 motility (*i.e.* all progressive motility). Antisperm antibodies were measured by the tray agglutination test (TAT) (Friberg, 1974). Follicle stimulating hormone (FSH), luteinising hormone (LH) and testosterone were assayed by standard techniques. The results of the wife's examination and tests were obtained from the gynaecology clinic. When appropriate, estimation of plasma progesterone to

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test ovulation was undertaken in our clinic. A record of the initial assessment and follow-up information has been kept on a computer file. A short questionnaire was sent each year to those couples who had moved or ceased to attend. Total follow-up was 2209 years, during which time 391 couples successfully conceived. The median follow-up for those couples who were unsuccessful was 29 months.

The pre-clinic trying time was defined as the time in months when the wife had been exposed to intercourse without the use of contraception before the first clinic visit. The total trying time at any given date was defined as the sum of the pre-clinic trying time and the interval between the first clinic visit and that date. The date of conception was calculated from the date of delivery less 9 months. If this date was not known, the date of conception was calculated as 2 months before the date on which the pregnancy was notified. In order to correct for concealed pregnancies, 2 months were subtracted from the follow-up of all couples who had not reported pregnancy.

Two different methods of statistical analysis were used. The couple-months method is a modification of ordinary life-table methods in which the number of months spent by each couple in each year of total trying time is calculated and added over all the couples in the study (Hargreave and Elton, 1983). The instantaneous fertility rate (fecundability) is then estimated for each year as the ratio of the number of pregnancies to the number of couple-months for that interval (Hargreave and Elton, 1985). In order to investigate prognostic factors, stratified couple-months analysis was carried out for groups of patients with different factor levels by comparing the observed pregnancies in each group wth those expected from the fecundability figures for all patients. A χ^2 test was then used for assessing statistical significance. A further refinement was to examine one prognostic factor while stratifying for another to see if the first factor gave significant prognostic information for given levels of the other.

The significance of prognostic factors was also evaluated by proportional hazards multiple regression (Cox, 1972) using the statistical package BMDP2L (Dixon, 1981). This method evaluates the prognostic significance of factors observed at the time of the first clinic visit in terms of their relationship to subsequent pregnancies. The four main factors used were pre-clinic trying time, sperm motility, sperm density (each categorised into six groups) and wife's status (categorised into five groups). The additional significance of further factors was tested by entering each factor as a continuous covariate. A χ^2 test with one degree of freedom was then used to test whether there was a trend in fertility as the factor varied for fixed levels of the other four main factors. This contrasted with a couple-months analysis in which the subsidiary factors were also categorised. A further important distinction between the two methods is that the couple-months analysis is based on strata of *total* trying time rather than *pre-clinic* trying time, thus making possible the analysis of pre-clinic trying time as a prognostic factor for fixed total trying time. This cannot easily be incorporated into the Cox analysis.

Results

This study confirms our earlier findings (Hargreave and Elton, 1983) that the total trying time is strongly related to subsequent fertility (Table 1). Tables 2 and 3 show the results of couple-months analysis of sperm motility and sperm density respectively, confirming that both of these factors give highly significant prognostic information after allowing for trying time. Cox analysis gives similar results for pre-clinic trying time alone ($\chi^2=70.18$, 5 df, $P<0.001$) and also for sperm motility ($\chi^2=55.24$, 5 df, $P<0.001$) and sperm density ($\chi^2=46.44$, 5 df, $P<0.001$) for given pre-clinic trying time. Tables 2 and 3 show that the major difference in prognosis for both sperm motility and density is between those with zero and those with positive values. Since there was substantial correlation between motility and density, we have also tested the prognostic value of each of these two factors

Table 1 Fertility Experience of Clinic Population According to Strata of Total trying Time

Total trying time (years)	*Couple-months*	*Pregnancies*	*Fecundability (%)*
0-1	171	8	4.68
1-2	2057	66	3.21
2-3	4311	100	2.32
3-4	4401	77	1.75
4-5	3813	49	1.29
5-6	3035	35	1.15
6-8	3719	31	0.83
8-10	2500	12	0.48
>10	1485	7	0.47
Total	25,492	385	1.51

(NB. Totals slightly less than those quoted for whole sample because in a few cases the trying time was not recorded)

Table 2 Couple-months Analysis for Strata of Motility (The motility was that recorded at the first clinic visit. Couples where the husband had azoospermia were excluded)

	Pregnancies		
Motility (%)	*Observed*	*Expected*	*O/E*
0	4	21.51	0.19
0.1 < 10	18	27.47	0.66
10 < 20	21	27.10	0.77
20 < 30	35	31.36	1.12
30 < 40	35	38.88	0.90
40 < 50	41	40.68	1.01
50 < 70	132	127.84	1.03
70 +	88	59.16	1.49

χ^2 (7 df) = 33.90 ($P < 0.001$)

Table 3 Couple-months Analysis for Strata of Density (The sperm density was that recorded at the first clinic visit)

	Pregnancies		
Density *(× 10⁶ ml)*	*Observed*	*Expected*	*O/E*
0	3	38.49	0.08
0.1 < 1	4	5.95	0.67
1 < 2	11	25.98	0.42
2 < 5	20	23.49	0.85
5 < 10	29	34.84	0.83
10 < 30	77	73.81	1.04
30 < 7	119	91.27	1.30
70 +	118	87.17	1.35

χ^2 (7 df) = 62.97 ($P < 0.001$)

while controlling for the other. Those with zero density were assumed for the purpose of analysis to have zero motility. The results show that motility gives significant additional information to density ($\chi^2 = 16.15$, 7 df, $P < 0.05$ by couple-months: $\chi^2 = 19.02$, 1 df, $P < 0.001$ by Cox), while density gives only a marginally significant prognosis when motility is taken into account ($\chi^2 = 11.56$, 7 df, NS by couple-months; $\chi^2 = 4.65$, 1 df, $P < 0.05$ by Cox). In our subsequent analysis we used sperm motile density (the product of sperm motility and sperm density) as a single factor to measure the combined influence of these two related factors.

Table 4 Couple-months Analysis of Wife's Status Stratified by Motile Density

	Pregnancies		
Wife's status	*Observed*	*Expected*	*O/E*
Laparoscopy and ovulation normal	95	126.25	0.75
No known problem	226	157.01	1.44
Ovulation problems but otherwise normal	17	21.89	0.78
Other problems including endometriosis, unilateral fallopian tube obstruction, scarring, chromosome abnormality	33	49.53	0.67
Bilateral fallopian tube blockage	6	22.32	0.27

($\chi^2 = 56.59$, 4 df ($P < 0.001$)

The results of the wife's tests have been divided into five categories and the couple-months analysis for these is shown in Table 4. The apparently good performance of couples where the wife had incomplete investigations is explained by a bias towards cases where pregnancy occurred after the first clinic assessment but before female investigations could be completed. Wives with bilateral fallopian tube obstruction were seen to have a poor prognosis. Cox analysis showed a similar highly significant effect of the wife's status for given pre-clinic trying time and motile density ($\chi^2 = 52.83$, 4 df, $P < 0.001$).

Table 5 shows the results of significance tests using both methods to test further factors for prognostic value while allowing for trying time, sperm motile density and wife's status. None of the fac-

Table 5 Chi-squared Statistics for Testing the Prognostic Significance of Further Factors While Allowing for Trying Time, Sperm Motile Density and Wife's Status

Possible prognostic factor	*Couple-months* χ^2 *(df) Sig*	*Cox regression* χ^2 *(df) Sig*
Husband's age	3.00(3) NS	0.95(1) NS
Wife's age	5.24(3) NS)	3.17(1) $P < 0.10$
Primary or secondary infertility	0.14(1) NS	0.05(1) NS
Best testis volume	1.60(3) NS	1.02(1) NS
Testis asymmetry	4.12(1) $P < 0.05$	5.78(1) $P < 0.005$
Presence of varicocele	1.23(1) NS	3.39(1) $P < 0.10$
Semen analysis		
Volume	4.51(3) NS	0.01(1) NS
% Normal	9.06(3) NS	0.71(1) NS
Serum TAT	0.90(2) NS	0.66(1) NS
Hormone measurements		
FSH	1.81(3) NS	3.87(1) $P < 0.05$
LH	0.47(3) NS	0.01(1) NS
Testosterone	2.91(3) NS	1.85(1) NS

Table 6 Details of Couple-months Analysis for Selected Factors From Table 5

Factor	*Level*	*Pregnancies* Observed	Expected	*O/E*
Wife's age at first clinic visit	<25	105	97.29	1.08
	25 <30	174	162.08	1.07
	30 <35	68	85.34	0.80
	35+	20	22.30	0.90
Testis Asymmetry	Present	59	46.16	1.28
	Absent	290	302.84	0.96
Varicocele	Present	103	93.77	1.10
	Absent	255	264.23	0.97
FSH	<3	141	136.64	1.03
	3 <6	145	141.49	1.02
	6 <12	65	67.68	0.96
	12+	13	18.19	0.71

tors tested showed a highly significant effect and only four gave results below the 10% level using Cox analysis. The details of couple-months analysis for these factors are given in Table 6, which shows that older wives and husbands with no testis asymmetry, no varicocele or a very high FSH tend to have a somewhat poorer prognosis than expected on the basis of the three main factors. Both LH and FSH showed highly significant prognostic effects when sperm motile density was not taken into account, but the results of Tables 5 and 6 show that this is accounted for by the association of high LH with poor quality sperm, while a small residual effect of high FSH remains even for given sperm motile density.

The relationship of wife's age to prognosis shown in Table 6 is much less strong than calculated by Lamb (1972). Table 7, which is similar to Table 1, is an alternative way of illustrating these data. Comparison of the figures in each row shows that older wives with a given total trying time are only a little less successful than their younger colleagues.

Table 7 Fecundability (%) in Relation to Total Trying Time for Couples Grouped by Wife's Age at First Clinic Visit

Total trying time (yrs)	*Wife's age at first clinic visit* <25	*25<30*	*30<35*	*35+*
0-1	(6.90)	(7.91)	(0.00)	(2.98)
1-2	4.16	2.12	2.94	9.67
2-3	2.17	2.57	2.31	0.61
3-4	1.53	2.25	1.16	1.49
4-5	1.40	1.43	0.89	1.09
5-6	1.35	1.04	1.40	0.00
6-8	0.64	1.30	0.48	0.41
8-10	0.62	0.27	0.83	0.00
>10	0.00	0.06	0.49	0.31

Figures in brackets are based on less than 5 couple-years.

Table 8 Fecundability (%) in Relation to Total Trying Time for Couples Grouped by Trying Time Prior to First Clinic Visit

Total trying time (yrs)	*<1*	*1<2*	*2<4*	*>4*	*All couples*
0-1	4.68	—	—	—	4.68
1-2	3.26	3.20	—	—	3.21
2-3	1.87	2.30	2.38	—	2.32
3-4	1.84	2.49	1.51	—	1.75
4-5	1.20	1.00	1.38	1.25	1.29
5-6	(0.00)	0.90	1.41	1.00	1.15
6-8	(4.63)	1.74	1.28	0.54	0.83
8-10	—	(0.00)	1.26	0.47	0.48
>10	—	—	(0.00)	0.48	0.47

Figures in brackets are based on less than 5 couple-years.

The couple-months analysis takes into account the total trying time but it is also possible to test the pre-clinic trying time as a prognostic factor (Table 8). If attendance at the clinic improves the chance of fertility, then couples with conditions which respond to treatment should succeed, leaving a residue of untreatable couples with a very poor prognosis. One way to examine if this is so is to compare couples with long follow-up who first attended the clinic a long time ago with other couples who have the same total trying time but who first attended recently. If clinic attendance is effective, this later group should do much better than those with the long follow-up. It can be seen from Table 8 that there was no significant result, suggesting that attendance at the clinic made little difference.

Finally, in Table 9 the results of treatment have been assessed using the couple-months analysis. There is no significant result, although for many of the treatment categories the numbers are too small to reach any conclusion. Clearly there is no outstanding treatment. It is possible that varicocele surgery and perhaps epidymovasostomy could show significant benefit if larger numbers were available.

Discussion

This study confirms and extends our previous findings (Hargreave and Elton, 1983). The duration of involuntary infertility, sperm motility, sperm den-

Table 9 Couple-months Analysis for 12 Months Following First Recorded Treatment After Initial Clinic Visit (Or After Initial Clinic Visit for Those With No Recorded Treatment

	Pregnancies		
	No.	*Observed*	*Expected*
Clomiphene	59	13	11.85
Mesterolone	71	15	18.57
Tamoxifen	17	4	2.83
Antibiotics	10	0	2.68
Steroids	37	7	7.20
Low dose Vit C	133	23	24.13
High dose Vit C	12	0	4.45
Varicocele surgery	55	14	12.22
Varicocele embol	11	1	0.84
Orchiopexy	5	0	0.05
Epididymovasostomy	16	2	0.31
AIH	2	1	1.61
Retro-ejaculation	4	0	0.22
None	477	120	109.88

sity and wife's status are all shown to be significant prognostic factors. These factors need to be taken into account when assessing the results of any infertility treatment for either male or female. When our series is larger and has a longer follow-up, it should be possible to refine the categories further or define new minor prognostic factors. Our main interest is in male infertility and our categorisation of female problems is relatively crude. For example, it should be possible in the future to analyse results according to degrees of endometriosis, types of ovulatory disorder and other categorisations of female problems. Nevertheless, the use of the present female categorisation allows a much more meaningful analysis of male results.

We cannot easily explain why our results for the wife's age are at a variance with previous reports (Lamb, 1972). A possible explanation is that our couples came to an infertility clinic and we have very little data from couples with trying times of less than 1 year. In Lamb's report at least half of the data was from couples during the first year of trying to conceive after stopping contraception. If this explanation is true it would suggest that the main effect of age is a delaying one and this delay is mainly seen in the first year. Another possible reason for the discrepancy could be that our clinic population was to some extent selected. Women with amenorrhoea or premature menopause would not necessarily have had their husbands referred for evaluation.

Two entirely different methods of statistical analysis have been used and the results agree. In our previous report (Hargreave and Elton, 1983) the couple-months method was used exclusively, but this was subsequently criticised on the grounds that it is relatively unsophisticated when compared with the Cox regression analysis. However, we believe that the couple-months method of analysis has the advantage of mathematical simplicity and that the result in terms of observed versus expected pregnancies can be readily understood by the clinician. The general agreement of results between the two methods validates the couple-months method.

Both sperm motility and sperm density have strong prognostic value, but motility gives better information. The practical implication is that efforts in the clinical seminology laboratory should concentrate on objective methods to evaluate motility. This would be more likely to help than improvement in sperm density measurement because density measurement is already a semi-objective technique.

It was disappointing to find that serum TAT gave no prognostic information and that the results of steroid treatment showed no benefit. This appears to cast doubt on the role played by antisperm antibodies in male infertility. However, both agglutinating and immobilising antibodies have been shown to occur significantly more often in an infertile male population than a fertile one (Hargreave *et al.*, 1980) and a highly selected group of patients was shown to benefit from treatment (Hargreave and Elton, 1982). Furthermore, immobilising antibodies have been shown to give a weak correlation with infertility (Hargreave *et al.*, 1980). The probable explanation for this paradox is that agglutinating antibodies detected by the TAT test do not directly cause infertility, but rather are a marker of patients likely to have other antibodies which interfere with fertility. Work is in progress to define antibodies that specifically interfere with fertilisation and to develop specific tests for these antibodies.

Apart from identifying major prognostic factors, the results of this analysis are disappointing. Two separate ways of looking at the results both indicate that our clinic has had little or no success in altering the expectation of fertility. Firstly, the information given in Table 8 shows that pregnancies occurred in the numbers that would be expected according to the total duration of infertility and that the event of coming to the clinic made no difference. Secondly, the results of the treatment analysis shown in Table 9 are inconclusive. It is possible that with larger numbers, varicocele surgery may be shown to give significant benefit, but the other results either show no effective treatment or the numbers are too small to draw any conclusion. Many of the patients included in this series were participants in randomised trials comparing non-specific hormonal or vitamin treatment for oligozoospermia (Scottish Infertility Group, 1982, 1984). These multicentre trials showed no difference between dissimilar treatments and we are therefore not surprised by our current findings. The conclusion is that non-specific treatment is palliative only and should therefore be prescribed only after consideration of cost and side effects.

Undoubtedly many couples are helped by a course of non-specific treatment for male infertility. In the past, however, clinicians have tended to raise false hopes because of a lack of appreciation of the natural prospects for fertility and a failure to distinguish these from supposed treatment successes. It is now possible to give most couples a realistic prognosis, but unfortunately there is no evidence of any successful treatment. Progress with male infertility is likely to occur only after realistic assessment of current results, greater efforts to reach a diagnosis and rigorous analysis of results using statistical methods which clearly distinguish treatment efficacy from background noise.

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The Authors

T. B. Hargreave, MS, FRCS, FRCSE, Senior Lecturer, University Department of Surgery/Urology.

B. McGowan, FRCSE, Urological Registrar.

Jennifer Harvey, BSc, Medical Laboratory Scientific Officer, University Department of Surgery/Urology.

Mary McParland, BA, AIMLS, Medical Laboratory Scientific Officer, University Department of Surgery/Urology.

R. A. Elton, BA, PhD, Senior Lecturer, Medical Computing and Statistics Unit.

Requests for reprints to: T. B. Hargreave, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

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Fecundability Rates from an Infertile Male Population

T. B. HARGREAVE and R. A. ELTON

University Department of Surgery/Urology, Western General Hospital, and Medical Computing and Statistics Unit, University Medical School, Edinburgh

Summary—From a computer file of 955 couples attending hospital because of an infertile marriage, 279 were identified where the female partner had normal investigation results. Follow-up information was available for all couples and the fecundability (conception rate per month) for the first year of follow-up has been calculated, stratified according to the husband's investigation results. The fecundability of couples where the wife had normal investigation results but the husband had reduced sperm density ranged from 0.4% for wives with azoospermic husbands to 5.9% when the husband had at least 10 million motile sperm/ml. For any given number of motile sperm the fecundability was also strongly dependent on the duration of involuntary infertility as recorded at the time of initial clinic attendance.

In view of the lack of effective treatment for most male infertility the fecundability rates reported herein are likely to represent those that would be found in an untreated population and should be useful as a base line when evaluating results of new treatments.

The fecundity rating (conception rate per cycle) or fecundability (conception rate per month) have been advocated for reporting the results of treatment for infertility (Kerin, 1979; Mudge, 1982). The purpose of this study was to report the fecundability rates in couples attending an infertility clinic where tests indicated a male problem. Most of the men had oligozoospermia but no evidence of specific endocrine defect. Non-specific treatment for men with idiopathic oligozoospermia is probably ineffective (Hargreave 1983a); therefore, despite the fact that many of the men in this series had non-specific treatment, the fecundability rates we report are likely to represent those that would be seen in an untreated infertile male population. These rates should be useful for comparison when assessing the results of new treatments for male infertility, including *in vitro* fertilisation (Cohen *et al.*, 1984).

Patients and Methods

Since 1978, all couples seen at our infertility clinic have been assessed in a standard manner and the results kept on a computer file. The history was taken from both partners by questionnaire (Hargreave, 1983b) and supplemented by interview. The husband was investigated in this clinic and the wife in one of several associated gynaecological clinics. Both partners were investigated (unless the husband was found to have azoospermia) and the results were recorded on the computer file. Follow-up was carried out both in the clinic and by questionnaire. Note was taken of any pregnancy and the date of conception calculated by subtracting 9 months. When the date of birth was not yet known the date of conception was assumed to be 2 months less than the date of the reported pregnancy.

The figures quoted in the results section were obtained directly from the computer record. The trying time (duration of involuntary infertility at the time of first consultation), the motile sperm density (millions of motile sperm per ml) and the status of the wife have already been identified as being of prognostic importance (Hargreave and Elton, 1983; Hargreave *et al.*, 1985). In this study our interest centred on those couples with an apparent male factor and therefore we identified

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Table 1 Fecundability in the First 12 Months of Follow-up for 279 Couples with Normal Wives (Wife's tests of Fallopian tube patency and ovulation normal, no endometriosis and no other known abnormality; husband's sperm motility and density known and follow-up information available)

Group		*No. of couples*	*Pregnancies*	*Months of follow-up*	*Fecundability (%)*
Azoospermic		21	1	240	0.4
Sperm motility and density	Trying time (months)				
0	<24	12	1	134	0.7
	25-48	11	1	130	0.8
	>48	4	0	48	0.0
0.01-2	<24	20	6	217	2.8
	25-48	13	4	146	2.7
	>48	10	0	113	0.0
2-10	<24	30	10	330	3.0
	25-48	18	7	187	3.7
	>48	9	2	102	2.0
>10	<24	75	42	717	5.9
	25-48	51	18	573	3.1
	>48	26	4	281	1.4
	Total	279	95	2978	3.2

couples according to whether the wife's investigations regarding ovulation and fallopian tube patency were normal, incomplete or abnormal. The following tests were accepted as evidence: laparoscopy for pelvic anatomy and for fallopian tube patency and endometrial biopsy or progesterone estimation for ovulation. In some cases hysterosalpingography was used in addition to laparoscopy and couples were excluded if there was any abnormality. Couples were also excluded if there was evidence of fallopian tube scarring, unilateral fallopian tube obstruction or endometriosis. Wives with endometriosis were excluded irrespective of the severity of the disease. Chromosome analysis was not routinely performed but the couple were excluded if the wife had a known chromosome abnormality.

Fecundability depends on the length of follow-up, since more fertile couples will be successful earlier, leaving a residue of less fertile couples. Treatment for male infertility usually lasts between 6 and 12 months. For this reason, and also because fecundability may change according to the length of follow-up, we report fecundability during the first year after clinic attendance only. We hope that these will be the most relevant figures with which to compare the results of new or apparently successful treatments. Also, in this analysis the couple were regarded as lost to follow-up at the start of artificial insemination by donor (AID), but this involved very few couples during the first year of clinic attendance because we did not accept couples investigated elsewhere and specifically referred for AID but only provided AID as part of a total programme of investigation and treatment.

Results

The computer file contained the records of 955 couples with a total follow-up of 2090 years. There were 279 couples where the wife had normal investigation results and where follow-up information was available. In all cases information was available on sperm density and sperm motility and the couple's trying time (duration of involuntary infertility at the time of presentation). The fecundability rating for the first year of follow-up for these 279 couples is shown in Table I, divided into groups according to motile sperm density and duration of involuntary infertility.

A further 476 couples were identified with male information and follow-up information but where the wife's investigations were incomplete, although there was no known abnormality. Couples were excluded if the wife's investigations showed any abnormality, even if these investigations were incomplete. The percentage of pregnancies recorded in the first year of follow-up from this group was greater than that from the group where the wife's tests were normal. This may be because although it was our intention to investigate the wife fully, the pregnancy was reported to us before the investi-

Table 2 Fecundability in the First 12 Months of Follow-up for 476 Couples where the Wife had no Known Problem (Wife's tests of Fallopian tube patency and ovulation incomplete but no abnormal results. Husband's sperm motility and density known and follow-up information available)

Group		*No. of couples*	*Pregnancies*	*Months of follow-up*	*Fecundability (%)*	*Combined fecundability from Tables 1 and 2*
Azoospermic		51	2	603	0.3	0.4
Sperm motility and density	Trying time (months)					
0	<24	34	2	392	0.5	0.6
	25-48	22	2	255	0.8	0.8
	>48	17	1	204	0.5	0.4
0.01-2	<24	41	19	417	4.6	4.0
	25-48	21	9	230	3.9	3.5
	>48	15	2	167	1.2	0.7
2-10	<24	54	34	495	6.9	5.3
	25-48	28	13	418	3.1	3.3
	>48	23	3	248	1.2	1.4
>10	<24	122	90	971	9.3	7.8
	25-48	58	39	515	7.6	5.2
	>48	31	12	334	3.6	2.6
	Totals	476	226	4647	4.9	4.2

gations could be completed. The fecundability relating to the husband's findings for this group is shown in Table 2. The fecundability for the two groups, *i.e.* wives with normal tests and wives with no known abnormality, are combined in the last column of Table 2.

Discussion

This study gives fecundability rates from a broad range of couples where the wife was normal according to investigations and where there may have been a male problem. It is difficult to obtain information from a large number of couples who have been followed up for 1 year with no treatment and indeed many of the men in our series did receive treatment. Thus the fecundability rates reported here may be better than would otherwise be seen.

How much are our results biased by successful treatment? The most common treatment was non-specific endocrine or vitamin supplement therapy for oligozoospermia, but despite randomisation between these dissimilar treatments there was no evidence of efficacy (Scottish Infertility Group, 1984). Our second most frequent treatment was varicocele ligation, but so far there is no evidence that this substantially improves fertility (Hargreave *et al.*, 1985). We calculate that 5 of the 226 pregnancies may have been the result of varicocele ligation. Because most varicocele patients were not improved we have chosen to include them in our analysis. Our fecundability rates may therefore be slightly higher than would be seen in a male infertility clinic population receiving no treatment.

Another factor which may affect our figures is the number of illegitimate pregnancies. Detailed paternity studies would be unethical and indeed the illegitimate pregnancy may on occasion be a happy solution for a couple where the husband is infertile. Some idea of illegitimacy may be obtained from Table 2, which shows that seven pregnancies were reported by 124 couples where the husband had either azoospermia or zero sperm motility. Treatment for obstructive azoospermia was thought to account for one pregnancy from a man with azoospermia. Two of the pregnancies in the zero motility group occurred after steroid treatment for immobilising antibodies. The remaining four pregnancies may have been illegitimate, although there was no indication of this. It is perhaps surprising how few unexplained pregnancies occurred in this group of 124 couples; this suggests that the illegitimacy rate was in fact low and presumably this would apply to other couples where the husband had better sperm measurements. It is worth noting that many couples who proceed to male infertility clinic investigations often remain loyal to each other despite years of disappointment. Our fecundability figures may therefore be biased by illegitimacy but only to a small extent.

Fecundability for couples where the wife had complete and normal tests is shown in Table 1, and where the wife had incomplete tests but no known abnormality in Table 2. If we exclude those couples where the wife had incomplete investigations, the fecundability stratified by male results as given in Table 1 may be lower than the true picture because the Table excludes those couples with more fertile wives who became pregnant before tests could be completed. The combined figures given in the last column of Table 2 may therefore represent a truer picture of the fecundability of couples stratified according to male factors. Tables 1 and 2 also show that there may be interaction between male and female fertility and that the more fertile wife can compensate for a husband's low sperm count. There is other evidence for such an interaction (Steinberger and Rodriguez-Rigau, 1983).

A fecundity rate of up to 25% has been reported in normal couples at an age when fertility should be maximal (Kerin, 1979). For a larger population irrespective of age the fecundability rate has been estimated at 10 to 20% for the first 2 years after stopping contraception (Vessey *et al.*, 1978; Smith and Cooke, 1985). The fecundity rating and fecundability rating are slightly different because one is based on menstrual cycles and the other on calendar months; nevertheless the two closely approximate, especially during a period limited to 12 calendar months. Our fecundability rates are clearly considerably depressed compared with normal, and this despite any bias to our figures from treatment or illegitimacy.

A fecundity rate of 20% has been reported from an AID clinic (Peek *et al.*, 1984). The main indication for AID is male infertility and in view of the fecundability rates which we report it is clearly effective. There is a need for effective treatment for male infertility but this is unlikely until more cases can be diagnosed. The most common finding is oligozoospermia and some clinicians erroneously assume that this is a diagnosis. The word is a description of the findings from semen analysis but gives no clue about the fundamental cause. The aetiology of oligozoospermia is one of the main challenges facing clinicians and reproductive biologists. The common treatment for idiopathic oligozoospermia is hormonal supplement despite the finding of a normal serum testosterone, but there is little evidence that it works (Hargreave, 1983a).

Because of the lack of evidence of any effect of non-specific treatment for male infertility it is probably justifiable to assume that our fecundability rates represent those that would be seen from an untreated male infertile population. It is hoped that these figures will be useful in the future when assessing the results of new treatments for male infertility.

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The Authors

T. B. Hargreave, MS, FRCS, FRCSE, Senior Lecturer, University Department of Surgery/Urology.

R. A. Elton, PhD, Senior Lecturer, Medical Computing and Statistics Unit.

Requests for reprints to: T. B. Hargreave, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

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Penile Hypercoagulability During Erection: a Possible Predisposing Factor to Ageing Penile Vascular Changes

M. S. BORNMAN, D. J. du PLESSIS, W. J. C. COETZEE and R. C. FRANZ

Departments of Urology and Surgery, University of Pretoria Medical School and the H. F. Verwoerd Hospital, Pretoria, South Africa

Summary—Haemostatic changes in the penile and systemic blood during erection were studied in the Chacma baboon. Dynamic hypercoagulability developed in the penile blood and fibrin was deposited on the endothelium of the penile artery and trabeculae during erection. These suggest that penile hypercoagulability predisposes to ageing penile vascular changes.

The erectile tissue of the penis consists of fibromuscular trabeculae protruding inwards from the tunica albuginea to form the corpora cavernosa (CC). The blood supply is through the deep penile artery, a branch of the internal pudendal. In order to obtain erection, an adequate blood flow rate and pressure head are required. As the intracavernous pressure starts to rise, penile rigidity sufficient for vaginal intromission develops. Arterial narrowing or occlusion can thus prevent erection and cause vasculogenic impotence (Zorgniotti and Rossi, 1980).

In man, ageing penile vascular changes consisting of intimal proliferation and fibrosis with narrowing of the lumen were described by Ruzbarsky and Michal (1977). Cohen *et al.* (1980) found that arteriosclerotic changes of the deep penile artery occur at an early age, even in sexually potent men, probably as a result of ageing. The polsters of Conti apparently have no physiological significance, but represent arteriosclerotic lesions (Benson *et al.*, 1981; Newman and Tchertkoff, 1980). Corresponding ageing changes were also demonstrated in the non-human primate and consisted of penile angiopathy and fibrous trabeculopathy with intertrabecular synechia (Bornman *et al.*, 1983).

The present study was designed to assess the importance of certain haemostatic changes as predisposing to ageing penile vascular impotence.

Material and Methods

The Chacma baboon (*Papio ursinus*) was chosen because of the close anatomical relationship with its human counterpart (Hampton and Matthews, 1966). Ketalar (ketamine hydrochloride) 10 mg/kg was used for induction of anaesthesia followed by Fluothane (halothane) 1.5–2% oxygen. After 20 min, erection was electrostimulated (Gould *et al.*, 1978) and maintained for 10 min. Two groups were studied and were comparable as far as diet, age and health were concerned.

Group A

Group A was subdivided into A1 and A2. In the first subgroup (A1), five baboons were stimulated and penile and systemic blood samples were collected for thrombo-elastography and for the determination of fibrinolytic activity (FA) in whole blood and plasma.

In the second subgroup (A2), four baboons, which had to be terminated for other reasons, were stimulated and full erections were maintained for 10 min. Directly thereafter 5000 units of heparin were administered intravenously to prevent iatrogenic induction of clotting. After 10 min, two biopsies of the CC were taken from each baboon. One biopsy was fixed in formalin (Bancroft and Stevens, 1977) and the other in glutaraldehyde (Franz and Coetzee, 1981) for light microscopy and scanning electron microscopy (SEM).

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The cavernous biopsies fixed in formalin were stained for fibrin and examined for the presence of fibrin on the endothelium of the deep penile arteries and trabecular surfaces. Glutaraldehyde-fixed specimens were prepared for SEM and similarly examined.

Group B

This group was also subdivided into B1 and B2. In subgroup B1, blood samples for thrombo-elastography were collected from five baboons during erection and masturbation. In subgroup B2, histological specimens were collected from four baboons after 10 min of full erection and masturbation and examined as in subgroup A2.

In both groups A and B, penile blood samples were drawn from the superficial dorsal vein of the penis. A no. 18 "Abbocath T" was introduced when full erection was obtained and sampling done at 2-min intervals. A 5 ml syringe, to which 0.25 ml of 9% tri-sodium citrate solution were added as anticoagulant, was used to draw blood from the catheter. The first 10 ml of blood were discarded before the sample was taken. Systemic blood was obtained from a peripheral vein on one of the limbs. One sample was taken before stimulation and then every 2 min from the time that a full erection was achieved.

It is important to note certain pitfalls in the collection of the blood samples. It is difficult to obtain sufficient penile blood from the dorsal vein of a flaccid penis without running the risk of damaging the vessel wall with liberation of tissue thromboplastin. Therefore the catheter was introduced only when complete erection was obtained.

Addition of the anticoagulant to the syringe was necessary in order to prevent clotting before the sample could be transferred to a test tube.

The thrombo-elastogram (TEG) provides a graphic representation of clot formation and fibrinolysis of whole blood *in vitro* (Franz and Coetzee, 1981). From the TEG parameters (r-time, k-time and maximal amplitude, Ma) the kinetic and dynamic coagulability can be calculated (Raby, 1975). Normal thrombo-elastographic values for baboons were determined using the systemic venous samples of 11 other healthy animals as controls.

Possible changes in FA of the penile blood during erection were studied using the euglobulin clot lysis time (ELT) of Von Kaulla (Von Kaulla and Schultz, 1958) the modified ^{125}I isotope method of Hickman (1971) and the diluted blood clot lysis time (DBCLT) of Fearnley (1965). Due to the unique circumstances of blood pooling and engorgement of the penis during erection, it was decided to evaluate FA mainly with respect to plasminogen activator activity (PAA), in the light of the widely held view that the activator is the pacesetter for fibrinolysis. The three practical and well proven methods for determining FA were chosen because they are also relatively inexpensive. The DBCLT and ELT evaluate the PAA of the plasmin system and are substrate-dependent methods. The DBCLT compared to the ELT also has the advantage that it incorporates the cellular component of blood.

It is now well established that polymorphnuclear leucocytes (PMNL) contribute significantly to the FA of whole blood (Moroz *et al.*, 1979). To compensate for possible abnormal high or low substrate (fibrinogen) concentration, the modified isotope method of Hickman (1971) was used because it determines the rate of fibrin breakdown in diluted whole blood clots and is not substrate-dependent. It also incorporates the cellular components of the blood.

Results

Normal thrombo-electographic values for baboons are shown in Table 1.

Table 1 Normal Thrombo-elastographic Values for Baboons

Parameter	Normal Values ($\bar{x} \pm 2$ SD) (n = 11)
r-time	4-15 mm
k-time	4-10 mm
Maximal amplitude (Ma)	38-51 mm
Index of thrombodynamic potential	(hypo-) 5-19 (hypercoagulable)
Thrombo-elastogram Index	(hyper-) 23-51 (hypocoagulable)

Group A

From the thrombo-elastogram measurements the index of thrombodynamic potential (ITP) was calculated, which represented the dynamic coagulability of blood (Raby, 1975). An ITP value above 19 signified dynamic hypercoagulability (Table 1).

The ITP changes of the penile blood during erection are shown in Table 2. The difference between the pre-stimulation values and the penile blood values at different intervals was statistically significant ($P < 0.05$) There was also a statistically signi-

Table 2 ITP Changes During Erection

	Systemic blood	*Penile blood*					
		Minutes after full erection					
Number	*Before stimulation*	0	2	4	6	8	10
1	13	19	19	25	30	19	10
2	7	29	29	39	40	39	20
3	9	15	16	25	37	25	26
4	17	26	44	28	24	27	28
5	11	11	20	23	22	20	16
P value	penile value compared with pre-stimulation value	<0.05	<0.02	<0.01	<0.01	<0.02	<0.05
P value	penile value compared with first penile sample		<0.01	<0.01	<0.02	<0.05	>0.4

ficant increase in the ITP of the penile blood compared with the initial values. The average increase exceeded the upper limit of the normal values (Table 1) and therefore thrombo-electographic hypercoagulability developed in the penile blood during erection. No change occurred in the ITP of systemic blood during erection (Table 3).

Table 3 ITP Changes in Systemic Blood During Erection

Number	*Before stimulation*	*Minutes after full erection* 0	2	4	6	8	10
1	13	17	13	6	2	5	6
2	7	12	12	19	20	18	17
3	9	4	3	11	11	12	11
4	17	8	10	10	12	10	12
5	11	10	12	10	14	9	11
P value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

The FA showed no statistically significant difference between the penile blood values at different times during erection and the systemic blood before stimulation (Table 4). Student's *t* test for paired statistics was used to evaluate all of the results.

Table 4 Results of Fibrinolytic Studies During Erection

Time of sampling after full erection	^{125}*I-isotope method (gradient)*	*Diluted blood clot lysis time (h)*	*Euglobulin clot lysis time (h)*
3 min	0.40	2.30	2.27
6 min	0.33	2.77	2.64
9 min	0.30	2.69	2.36

No statistically significant changes occurred ($P > 0.05$). Mean values ($n = 5$).

With light microscopy, fibrin deposits were found on the endothelium of the deep penile artery as well as on the trabecular surface of subgroup A2. With SEM, fibrin strands could be demonstrated on both endothelial layers (Fig.).

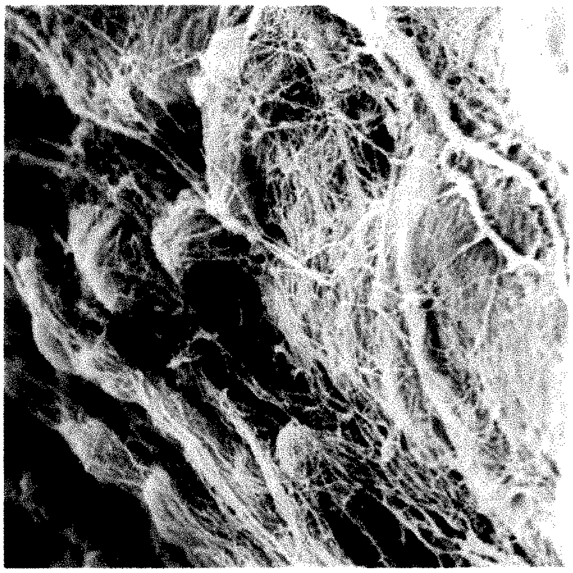

Fig. Scanning electron microscopy of the corpus cavernosum. Fibrin strands almost covered the endothelium.

Group B

The results of erection and masturbation (subgroup B1) are shown in Table 5.

The difference between the systemic pre-stimulation value and the penile value at the different intervals was statistically significant ($P < 0.05$). Using

Table 5 ITP Changes During Erection and Masturbation

	Systemic blood	*Penile blood*					
		Minutes after full erection					
Number	*Before stimulation*	0	2	4	6	8	10
1	15	28	48	59	50	50	51
2	15	5	29	27	24	28	33
3	13	6	12	14	18	14	14
4	12	10	22	23	20	27	24
5	10	22	28	33	42	21	28
P value	penile value compared with pre-stimulation value	> 70.05	< 0.05	< 0.05	< 0.02	< 0.02	< 0.02
P value	penile value compared with first penile sample		< 0.005	< 0.01	< 0.005	< 0.01	< 0.01

the first penile value as baseline, a statistically significant increase in the penile ITP was found ($P < 0.05$). Therefore thrombo-elastrographic hypercoagulability developed in the penile blood also during erection and masturbation.

Histological examination of the corpora cavernosa during erection and masturbation (subgroup B2) showed fibrin deposits on both the endothelium of the penile artery and trabeculae, as in subgroup A2.

Discussion

In 1856 Virchow stated that stasis, intimal damage and hypercoagulability are predisposing factors in the pathogenesis of venous thrombosis. True stasis in the penis during erection has not yet been proved, but for rigidity to develop a sufficient increase of pressure in the CC is necessary. Pressure can only rise when there is "relative obstruction" to the outflow. It also implies that the CC are filled to their maximum and that "relative stasis" may therefore occur.

The causes and development of hypercoagulability are multifactorial. According to Hirsh (1977), it implies that changes can be detected in blood which can be used to predict the possible onset of thrombogenesis, although hypercoagulability *per se* is not synonymous with thrombogenesis (Franz and Coetzee, 1981). Thrombo-elastographic hypercoagulability developed only intracavernously and not systemically. This may be the result of the rapid dilution of the factors responsible for the hypercoagulability into the systemic blood or inactivation of activated clotting factors by the liver. The possible relationship between hypercoagulability and thrombogenesis may be that of the "relative stasis" and prolonged exposure of blood to the endothelium of the CC could trigger the transgression of a hypercoagulable into a thrombotic state. These components may all be directly or indirectly involved in the generation of thrombin, which is the key initiating substance of thrombogenesis.

In the recent literature the prominent role of prostacycline (PGI_2) and thromboxane (TXA_2) in haemostasis is very interesting and should not be overlooked as a possible link between hypercoagulability and thrombogenesis. PGI_2 is the main prostaglandin produced by vascular endothelium and is a potent vasodilator and inhibitor of platelet adhesion. The concentration of PGI_2 has a fixed ratio to another important prostaglandin, thromboxane (TXA_2), which is a potent vasoconstrictor and potentiates platelet adhesion and aggregation (Jacobs and Knottenbelt, 1983). Increase in the concentration of TXA_2 as a result of platelet release will therefore promote the aggregation of platelets and may contribute to hypercoagulability. To make the situation even more complex, the possible role of PF 1–7 must also be considered.

As a result of congestion of the penis during erection, one would expect an increment in PA release similar to the well documented rise after venous occlusion. The fibrin deposited during erection may therefore cause an imbalance between fibrin formation and fibrinolysis. If fibrin is not completely removed from the endothelium, infiltration by fibroblasts will follow. Fibroblastic activity leads to collagen production and eventually to fibrosis. Endothelial proliferation is followed by the gradual narrowing of the supplying artery (a peripheral penile angiopathy) as well as a fibrous trabeculopathy.

Although the exact mechanism of hypercoagulability and fibrin deposition in the penis during erection remains conjectural, it would seem that undue fibrin deposits, as a result of hypercoagulability or defective fibrinolytic mechanism during erection, may contribute to the pathogenesis of ageing vascular impotence. Clearly there are considerable individual variations and by limiting the exposure to factors known to cause hypercoagulability such as obesity and diabetes mellitus (Franz and Coetzee, 1981), cigarette smoking (Howland *et al.*, 1974), and stress (Pollar *et al.*, 1970), potency may be preserved well into advanced age.

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The Authors

M. S. Bornman, MBCLB, DSc(Pret), formerly Senior Lecturer, Department of Urology, University of Pretoria. Now Consultant for Andrology, Department of Urology, Medunsa, and Senior Research Officer, Roodeplaat Research Laboratories, Sinoville, Pretoria.

D. J. du Plessis, MMed(Urol)(Pret), FCS(SA), Professor and Head, Department of Urology, University of Pretoria.

W. J. C. Coetzee, DSc(Pret), SciNat(SA), Professor and Head, Stomatological Research Centre, Department of Dentistry, University of Pretoria.

R. C. Franz, MMed(Chir)(Pret), Professor, Department of Surgery, University of Pretoria.

Requests for reprints to: M. S. Bornman, Roodeplaat Research Laboratories, P.O. Box 13873, Sinoville 0129, Pretoria, Republic of South Africa.

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Assessment of Collagen Film for Use in Urinary Tract Surgery

R. SCOTT, R. BARAZA, S. D. GORHAM, I. McGREGOR and D. A. FRENCH

Department of Urology, Royal Infirmary, Glasgow

Summary—This investigation assessed a biodegradable collagen membrane which can be sutured around the ureter to prevent urine leakage, thus permitting healing to proceed more rapidly while the membrane itself is resorbed.

Following an early *in vitro* investigation in which collagen was assessed, a more comprehensive survey has now been carried out. Tissue compatibility and biodegradation were assessed by implanting the film into the lumbar muscles of rats; it was then used to cover experimental ureterotomies in New Zealand White rabbits.

The data obtained from the rabbits confirmed that a collagen membrane can prevent leakage of urine from the ureter during healing while it itself is biodegraded, indicating that a collagen membrane could be used to repair the injured urinary tract.

When the urinary tract is opened, either accidentally or deliberately, it may heal spontaneously. However, leakage may take place and cause a urinoma, which may become infected and cause a fistula. After operation, urine is removed by a drain. Anything which reduces the leakage of urine and allows wound closure to proceed more rapidly would reduce the patient's stay in hospital. A biodegradable membrane applied around the operation site could well hasten the healing process. Such a membrane should be leakproof, non-toxic, non-antigenic, strong and elastic, and it should not allow the precipitation of calcium salts in the urinary tract. The membrane should be resorbed as rapidly as possible after fulfilling its intended function. One such material is collagen, which constitutes 33% of the total body protein and forms the major structural components of a diverse range of connective tissues (Lapiere and Nusgens, 1976; von der Mark, 1981). Because of its high tensile strength, biodegradability, haemostatic properties (Chvapil *et al.*, 1973), low antigenicity (Etherington *et al.*, 1979), non-cytotoxicity and ability to support cellular growth (Shakespeare and Griffiths, 1980; Oliver *et al.*, 1982), collagen has already found many applications in the biomedical field (Dagalakis *et al.*, 1980; Yannas and Burke, 1980; Holl-Allen, 1984; Kamer and Churukian, 1984; Stein *et al.*, 1985).

Recent *in vitro* studies have shown bovine collagen to be leakproof, to be compatible with human urine and resistant to the degradative effects of tissue homogenates, and it did not appear to act as a nidus for the crystallisation of urinary salts (Gorham *et al.*, 1984).

Materials and Methods

All surgical sutures were supplied by Ethicon Ltd., Edinburgh.

In vitro Studies

The collagen film was prepared by the method of Gorham *et al.* (1984), except that a 0.4% suspension of collagen was used. This higher concentration was chosen because the original membrane did not have sufficient strength to hold a suture. After

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Read at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

cutting to the required size, the collagen film was sterilised by washing in 70% ethanol and was subsequently stored in phosphate buffered saline solution containing 300 iu/ml penicillin and 300 µg/ml streptomycin (Etherington *et al.*, 1979).

In vivo Studies

(*i*) *Sprague-Dawley Rats.* Under anaesthesia, a median longitudinal incision was made and a small pouch produced with a Beaver blade. Samples of film (2 × 10 mm) were implanted into the lumbar muscles and the pouches closed. At post-mortem the whole muscle from the marker stitch forward was removed, fixed in 10% buffered formalin and processed for routine histology.

(*ii*) *New Zealand White Rabbits.* The rabbits, which were studied in two groups, were maintained on standard laboratory diet. They were anaesthetised with 0.75 ml Sagatal (a 600 mg/ml solution of sodium pentabarbitone) administered intravenously through the marginal ear vein. Anaesthesia was maintained by a mixture of oxygen, nitrous oxide and halothane. The animals were sacrificed by the administration of 1 ml Euthatal (a 200 mg/ml solution of sodium pentabarbitone).

Group I (19 Rabbits)

The kidney and upper ureter were approached via an extraperitoneal incision and the kidney delivered into the wound. The right ureter was cleared of fat and opened. A fine probe was inserted to confirm that the lumen had been identified. A small piece of collagen film (1 × 1.5 cm) was placed over the ureterotomy and sutured to itself with two 3/0 chromic catgut sutures. The wound was closed in three layers without drainage. As a control the left ureter was similarly exposed and a membrane sutured around the organ as previously without opening the ureter.

Two further experiments were carried out. In the first, the left ureter was exposed but in no way interfered with; in the second, the right ureter was exposed and opened. In neither case was a collagen membrane applied. These animals were sacrificed after 1 week.

Animals were sacrificed over a 13-week period and the ureters examined histologically using haematoxylin, phloxine and saffron (HPS trichrome) staining. Any calcification was verified using the von-Kossa (silver deposition) stain.

Group II (26 Rabbits)

The experiment was repeated with a second group of animals with the following modifications. A larger piece of film (2 × 1.5 cm) was used and it was actually wrapped around the ureter and stitched to itself using Ethilon 6/0 non-degradable sutures to mark the site off operation. Ampicillin (75 mg) was administered daily to the animals for the first 5 post-operative days. The animals were sacrificed over a 15-week period. As described in Group I, four rabbits were used in sham operations in which membrane was not used. These animals were sacrificed after 6 days and 4 weeks.

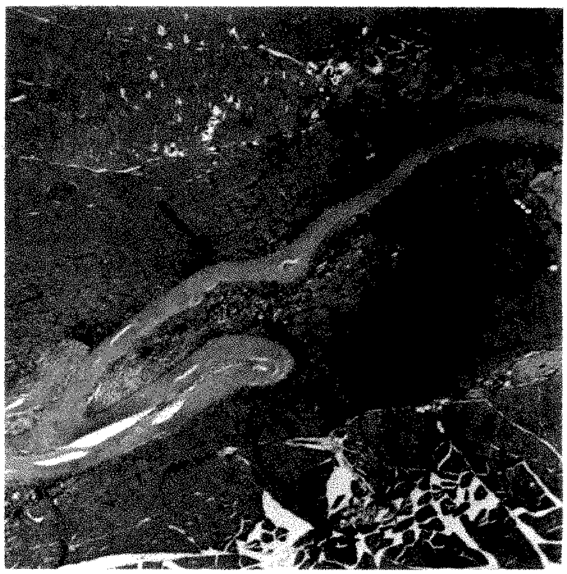

Fig. 1 Collagen film 7 days after implantation into the lumbar muscle of a Sprague-Dawley rat. The implant shows appreciable cellular activity, mainly around the periphery, much of which is the result of post-operative trauma. Some degradation of the membrane is becoming apparent, particularly at the ends, which are starting to be split open. (HPS trichrome × 12.5).

Results

In vivo Studies

(*i*) *Sprague-Dawley Rats.* Figures 1 and 2 show the film at 7 and 49 days after implantation respectively. Although the rate of biodegradation of the film varied among different animals, the general pattern of absorption was similar. Initially, the cell population surrounding the films tended to be mainly polymorphic with some macrophages and a few fibroblasts. After 7 days the cells most in evidence were macrophages and the films began to show signs of being absorbed, particularly at the ends, which split open into ribbons. This pattern of degradation continued over the implant period of

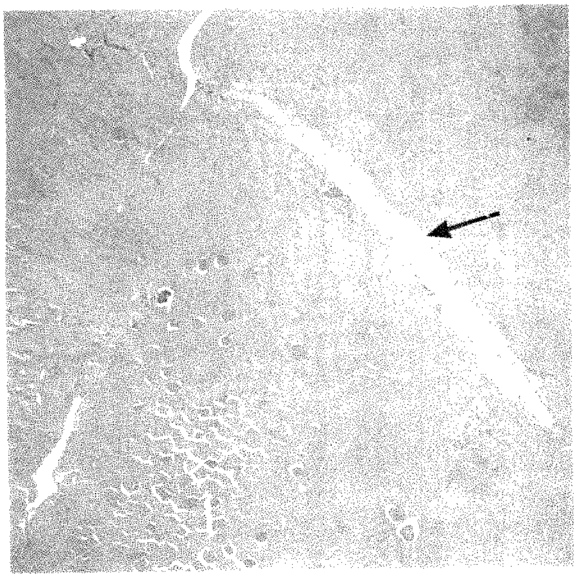

Fig. 2 Collagen implant 49 days after implantation into the lumbar muscle of a Sprague-Dawley rat. The section shows minimal cellular activity around the edges but the collagen, which is considerably diminished by this stage, has become infiltrated by macrophages. (HPS trichrome × 12.5)

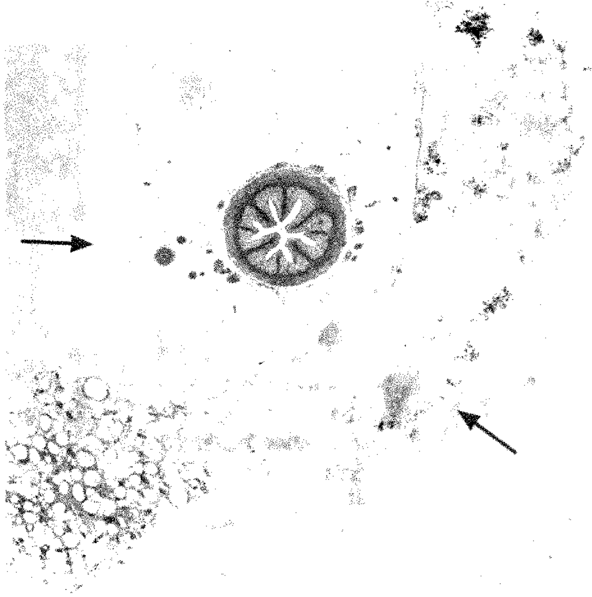

Fig. 3 Section of ureter from sham operation revealing normal structure surrounded by loose areolar tissue contained within a natural collagen capsule. (HPS trichrome × 12.5).

up to 70 days, when some identifiable residues were still present. Taking account of the initial trauma caused by surgery, the tissue reaction was slight.

(*ii*) *New Zealand White Rabbits*

Macroscopic Findings—The macroscopic findings from the two groups of animals are summarised in the Table. The severity of infection and abscess was considerably less in the second group because antibiotics were used. In those animals in which a sham operation was undertaken, *i.e.*, no membrane was applied to the ureterotomy, the expected urinomas occurred.

Histological Findings—A section from a control animal in which no membrane was used reveals that in the rabbit there is a natural layer of collagen separated from the ureteric muscle by loose areolar tissue (Fig. 3).

Table Comparison of Macroscopic Findings in Two Groups of New Zealand White Rabbits

	Group I (17 animals)	*Group II (22 animals)*
Abscess	7 (41.2%)	5 (22.1%)
Infection	1 (5.9%)	2 (9.0%)
Urinoma	5 (29.0%)	5 (22.7%)
Leakage	1 (5.9%)	0
Unaffected	7 (41.2%)	10 (45.5%)

These figures indicate a lesser degree of infection in the Group II animals, which received antibiotics.

The results obtained from the group II animals may be summarised as follows. Up to 1 week post-operatively the material shows no sign of breakdown (Fig. 4) and the reaction is principally polymorphonuclear leucocytes with a few mononuclear

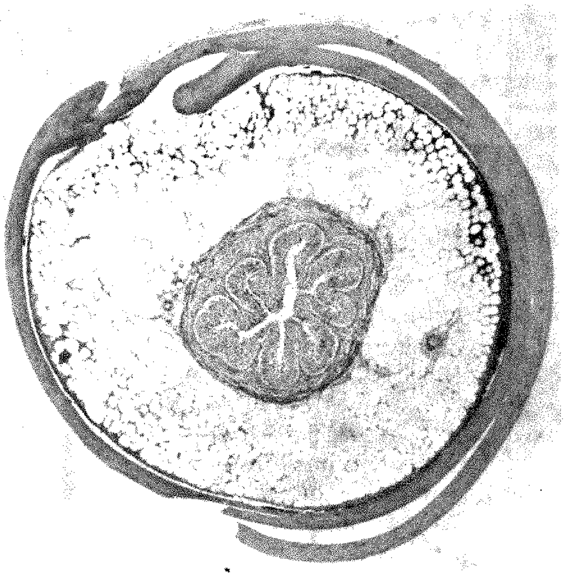

Fig. 4 Section 2 days post-operatively. The membrane can be readily identified around the ureter. No sign of resorption can be seen at this early stage. (HPS trichrome × 12.5).

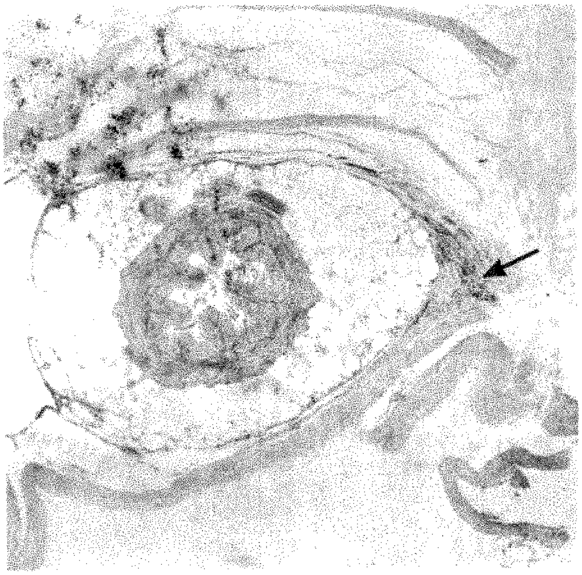

Fig. 5 Animal 3 weeks after operation. The membrane is splitting and is infiltrated by phagocytes with minimal peri-ureteric inflammatory reaction. (HPS trichrome × 12.5).

cells. A considerable part of the reaction is due to operative trauma.

Between 1 and 8 weeks the collagen implant shows progressive infiltration by cells which are principally mononuclear histiocytic in type; polymorph leucocytes, if present, are few. The reaction also becomes histiocytic or in some cases fibrotic during this period (Fig. 5). There was one instance of a marked giant cell reaction that was almost sarcoid in type. Towards the end of this period it becomes increasingly difficult to distinguish between the collagen of the implant and pre-existing animal collagen in uncomplicated cases.

After 8 weeks there is little obvious change but the difficulty in distinguishing host from implant collagen becomes progressively greater.

In the first series of experiments it was difficult to draw any significant conclusions regarding the biodegradation of the membrane because the absence of a marker suture made it difficult to identify the exact site of operation and because frequent and severe infections gave rise to excessive collagenous scar tissue in many cases.

Discussion

In many urological operations the urinary tract is opened and leakage of urine can prolong the healing process. The use of synthetic materials is attractive but is difficult because it may induce precipitation of calcium salts and stricture formation (Donovan and Barrett, unpublished data). The use of a biologically derived material reduces the likelihood of these complications but raises problems of antigenicity and rejection. Collagen, which has a high tensile strength and is impervious to urine, may overcome many of these problems. Its biochemical and physical properties make it interesting as a potential repair agent for the urinary tract (Gorham *et al.*, 1984) and the results of implant studies on rats were sufficiently encouraging for it to be used in rabbits.

In the present experiments, complications were largely caused by not using a drain after creating a ureterotomy. In humans, of course, a drain would always be inserted. Problems caused by infection in the Group I animals were eliminated in the second group by antibiotics.

The development of biodegradable materials is exciting and has recently been shown to be feasible in the experimental healing of fractures (Rokkanen *et al.*, 1985).

The current experiments indicate that collagen film is capable of preventing leakage from the urinary tract, that it is biodegradable and disappears without trace, and that it has a high tensile strength but is also pliable and elastic enough to allow continued function of the ureter during healing. The results are encouraging and suggest that this type of material may well assist urinary tract repair following surgical intervention.

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The Authors

R. Scott, JP, MD, FRCS(G), FRCSE, Senior Consultant Urologist, Royal Infirmary, Glasgow.

R. Baraza, FRCSE, Consultant Urologist, Kenyatta Hospital, Nairobi, Kenya.

S. D. Gorham, BSc, PhD, CChem, MRSC, Research Biochemist, Devro Ltd., Glasgow.

I. McGregor, LRSC, Research Assistant, Devro Ltd., Glasgow.

D. A. French, BSc, Senior Biologist, Ethicon Ltd., Edinburgh.

Requests for reprints to: R. Scott, Department of Urology, Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ER.

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Evaluation of Light Sources and Light Guides for Use in Transurethral Surgery

M. G. PEPPER and P. J. MOUNTFORD

Medical Physics Department, Kent and Canterbury Hospital, Canterbury

Summary—An evaluation of the quality of light sources and guides was carried out in response to a demand that sufficient light intensity should always be available for transurethral procedures when bleeding occurs. A light monitor was developed for the rapid assessment of the source intensity and light guide transmission. A simple test protocol was also developed for routine assessment of the sources and guides and for evaluation of new sources and guides before purchase. The sources and guides were classified in order of merit and coded to permit the selection of those of the highest quality; this guarantees a satisfactory level of illumination during surgery.

Ease and success of operation during transurethral surgery depends upon the surgeon having adequate illumination of the site of operation. The quality of illumination depends upon the endoscope system being used both for the transmitted light reaching the site and the reflected light reaching the surgeon's eye. The intensity of reflected light is greatly reduced when bleeding occurs and the quickest and most simple way to increase the reflected light intensity is by increasing the electrical power to the lamp. Thus, before bleeding starts, there must be adequate illumination without the lamp being operated at full power. Because of differences in the power of different sources and in the transmission of different light guides, due to such causes as ageing, fibre damage and type, this latter criterion was occasionally not met during operative procedures, causing inconvenience and frustration as the cause of lack of source illumination was not readily identifiable. Thus it was desirable for the theatre staff to be able to select combinations of source and light guides which would satisfy the above conditions.

A simple, inexpensive light meter has been constructed and a basic test procedure developed to make relative measurements of the output of the light sources and to measure the relative transmission of the guides. This report describes the meter, the test procedure for assessing and routinely checking the performance of the sources and guides, reports some measurements of this performance and identifies an acceptable level of illumination for transurethral surgery. The telescopes were not included in the test procedure because any damage was easily detected by visual inspection.

Materials and Methods

The Meter The meter was constructed so that it could be used for measuring both light source and light guide transmissions. Light passed down a stainless steel collection tube which was designed so that when mounted in the source, its aperture was at approximately the same distance from the lamp as the end of an inserted light guide. The distal end of the guide could also be located inside the end of the tube to permit measurement of the relative transmission of the guide. The source and guide connections were of the "Storz" type. The light was detected by a Gallium Arsenide Phosphorous Schottky type photodiode (Hamamatsu G1126). This detector was chosen because it does not respond to the infra-red content of the radiation emitted by the light source (Mountford and Pepper, 1981). The diode was operated in its linear photocurrent mode with a 10 ohm resistor converting the photocurrent to a voltage (Fig.). This resistor was selected to produce as large a voltage as possible for the maximum intensity available for the light sources without overloading the display digital voltmeter (RS 258-114 or 258-041). The voltage was displayed in arbitrary units as only rela-

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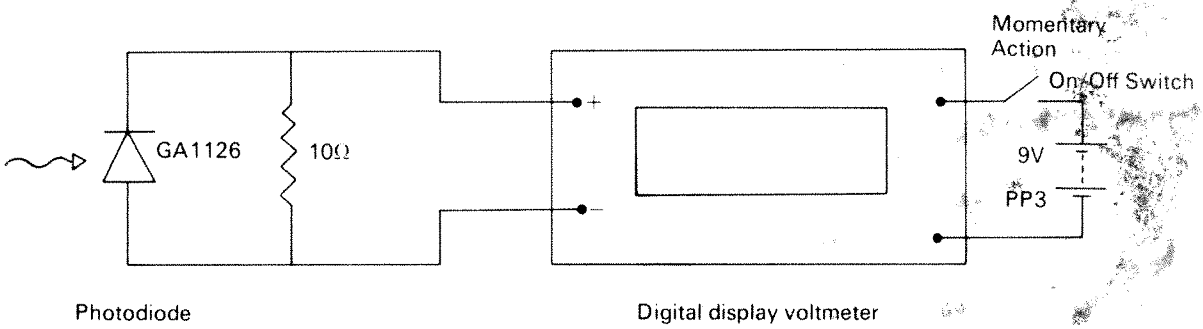

Fig. Light monitor circuit.

tive measurements of light intensity were made. The light meter was operated by a momentary action push button switch to preserve battery life. The power source was a 9 V PP3 battery with a life of more than a year at the operating current of 50 μA.

Light Sources Six light sources of four different types were tested (Table 1). After the initial measurements the mirror, bulb and aperture of the sources were realigned as appropriate to produce the optimum measured output for the exit apertures (see Results section).

Table 1 Lamp Type and Typical Performance

Lamp type	*Number*	*Bulbs power (watts)*	*Type*	*Reflector*	*Typical max output*
1*	2*	100	A1/231**	External	80
2	1	150	A1/211	Internal	220
3	1	100	A1/231**	External	80
4	1	150	A1/211	Internal	140

*This lamp used a mirror to reflect the light through 90° on to the exit apertures.
** A1/231 operates on the tungsten halogen principle.

Light Guide Measurements Measurements were made of the relative transmission properties of flexible light guides from three different suppliers of 2.5 mm and 3 mm diameter and of similar age. The output of one of the light sources was adjusted until a value of 100 was obtained on the meter. The light guide was then attached to the light source and the light transmitted by the guide was measured with the meter, enabling a transmission factor to be calculated. This was a relative measurement because the light collection efficiency of the meter tube was not the same as that of the entrance face of the light guide, the spatial distribution of the light differs at the proximal and distal ends of the guide, and because the spectral transmission properties of the guide were wavelength-dependent. Measurements were also carried out on new unused guides of 3.5 mm diameter from the suppliers.

Tests in Theatre Using several different combinations of sources and guides, an acceptable level of illumination was determined by a surgeon during transurethral surgery.

Results

Light Sources The output from all sources was dependent on the aperture selected. The difference in aperture output was greatest in light source type 1, where a mirror was used to direct the light from the lamp on to the exit apertures. In adjusting the alignment to improve the output, a choice had to be made between maximising the output at one aperture or optimising the output so that there was equal intensity at both apertures. The optimum output for types 3 and 4 was approximately the same as the maximum available, whereas for type 1 the optimum output was only one-half to one-third of the maximum available. With one type 2 source the exit aperture had loosened and was misaligned by approximately 5 mm. Realignment led to a six-fold increase in output. In another type 2 source the bulb was not pressed home into its socket and depressing the bulb by approximately 5 mm led to a two-fold increase in light output. The rheostat controls on the type 1 sources could not provide a fine control, and when moved between positions 7 and 8 the output would decrease and then increase by a factor of five. A further problem was that the light output at the maximum setting of 12 was less by a factor of two than that obtained at a setting of 10. These effects were due to the physical construction of the rheostat windings. The maximum output obtainable from the sources is given in Table 1. It can be seen that type 1 in general provided a lower output than older types (2, 3 and 4) and thus physical appearance should not necessarily be used as a criterion in selecting a source. This was due to the older types having a direct optical path between the bulb and the exit aperture, whereas type 1 used a mirror to reflect light from the bulb through 90° on to the aperture.

Light Guides The relative transmissions of the used and new light guides are given in Table 2. The proximal faces of the two of the guides with transmissions of less than 15% had been partially melted, presumably due to overheating within the light source.

Table 2 Relative transmission properties of 19 new and unused guides

Relative transmission (%)	*Diameter (mm)*	*Supplier*	*Comment*
>25	3.5	1	Three new, two in use
20-24	3.5	2	One new
15-19	3.5	2+3	One new, four in use
	2.5	1	Two new, two in use
<15	3.5	3	Two new, two in use

Tests in Theatre Guides with a minimum relative transmission factor of 15% provided adequate illumination under conditions of bleeding when used with any of the light sources at maximum intensity (after realignment of the sources as described above). Neither of the guides with melted faces transmitted an acceptable level of illumination.

Discussion

Before this study, the criterion for selecting a light source for use in theatre was that of physical appearance, on the assumption that the most recently purchased sources would provide the highest output. It was found that this criterion was inappropriate and that evaluation of source quality was essential, since manufacturers may concentrate on aesthetic appearance rather than output performance. This study also showed that the lamp and apertures must be aligned correctly. This precaution was particularly important for type 2, where the aperture plate can loosen and where the lamp may not be correctly seated in its base.

The results of the light guide tests made it possible to grade them into four categories (Table 2). A band of coloured tape was fitted to each guide to permit rapid selection of the highest quality guide. Only the 3.5 mm diameter guides from supplier 1 had a relative transmission greater than 25%, whilst those from supplier 2 were in the 17 to 20% range. It was also noted that the 2.5 mm diameter guides from supplier 1 were in the same transmission range as the 3.5 mm diameter guides from supplier 2. The measurements and visual inspection of the new, unused 3.5 mm guides from the two suppliers supported these conclusions.

The results indicated that problems which had arisen in theatre were due to the selection of a damaged guide or the combination of a lower quality guide (15-20% transmission) and a source with a misaligned lamp and aperture. Selection of the best quality guides and correctly aligned sources should guarantee adequate illumination under all conditions.

This study has also indicated the need for regularly checking the quality of the light sources and guides. A simple coding system has enabled the theatre staff to select the best guides from their stock and thus prevent unnecessary and irritating delays during surgery. It has also been possible to use the light monitor to evaluate the quality of light guides from different suppliers and to purchase accordingly.

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The Authors

M. G. Pepper, PhD, Lecturer in Medical Electronics, University of Kent; Principal Physicist, Medical Physics Department, Kent and Canterbury Hospital.

P. J. Mountford, PhD, MInstP, Principal Physicist, Medical Physics Department, Kent and Canterbury Hospital.

Requests for reprints to: M. G. Pepper, Department of Medical Physics, Kent and Canterbury Hospital, Canterbury, Kent CT1 3NG.

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Significance of Dipstick Haematuria. 1. Correlation with Microscopy of the Urine

J. P. ARM, E. B. PEILE, D. J. RAINFORD, P. W. STRIKE and R. E. TETTMAR

Department of Renal Medicine; Institute of Pathology and Tropical Medicine, PM RAF Hospital, Halton, Aylesbury

Summary—The reliability of a chemical test for haematuria has been evaluated in patients referred for investigation of suspected renal or urological disease. Red blood cells in concentrations of 10/µl or greater were found in 24% of urines giving a negative dipstick result, 82% of urines giving a trace positive result and nearly 100% of urines giving dipstick results greater than this. The accuracy of the reagent strip in predicting the presence or absence of significant haematuria was improved by testing several urines from each patient. On the basis of this study, if significant haematuria is present, reagent strip urine testing is an efficient method for its detection.

Haematuria, whether macroscopic or microscopic, may be a sign of serious renal or urological disease. Various methods are available for its detection. Examination of the urinary deposit after centrifugation is widely used but is subject to many errors and is often delegated to the most junior members of laboratory staff. Furthermore, standard methods and well established reference ranges are seldom used. Thus microscopic haematuria may easily be missed and when found in small quantities the question arises as to its significance. Red cell counts of unspun urine are more accurate, especially if phase contrast microscopy is used. Such methods are, however, time-consuming and rarely used as a routine in the laboratory or ward. Chemical tests are more convenient and widely used but earlier evidence suggested that they were too insensitive (Freni *et al.*, 1977). These tests have since been refined and now appear more promising. Patients are often referred for a consultant opinion because they have been found to have "dipstick haematuria" at a routine medical examination. Often the test has been only trace positive and the referring doctor questions the accuracy of such results, thinking that the dipstick may be oversensitive. This study was designed to evaluate one of the more recently available chemical tests, N-Multistix-SG (Ames Co). The results of the reagent strips were correlated with red cell counts of unspun urine using phase contrast microscopy, and with pathology.

Patients and Methods

One hundred patients were admitted to the study between January 1982 and June 1983. They included both civilians and armed forces personnel from amongst our routine admissions. They were selected on the basis of a knowledge or suspicion that haematuria was present, and the expectation that they would be on the ward long enough to complete the protocol at a time when the laboratory would be able to handle the workload generated. Consequently the patients were not consecutive admissions, as mid-week admissions were not entered into the trial and normally no more than two patients could be studied in any one week.

Each patient was asked to provide nine fresh clean mid-stream specimens of urine. A member of the trained nursing staff decanted part of each urine into a sterile container for the laboratory, whilst the remaining aliquot of urine was tested with an N-Multistix-SG reagent strip. The results were scored as negative, haemolysed trace, non-haemolysed trace, +, + +, or + + +. Three speci-

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mens, early morning, mid-morning, and early afternoon, were collected on three consecutive days and examined in the laboratory as soon as possible. In the laboratory the specimen was gently mixed and samples taken for culture, cell count and further testing with the reagent strip. The cell count was performed on unspun urine under phase contrast microscopy using an Improved Neubauer counting chamber, the results being expressed in red cells per microlitre (RBC/μl). Each large square in the chamber represents 0.1 μl and counts were based on the examination of two such squares. Hence one red cell in two large squares represents 5 RBC/μl and results are therefore reported in multiples of 5. Testing on the ward and in the laboratory was entirely independent, ward staff and laboratory staff being unaware of each other's findings during the patient's stay.

Routine tests on all patients included three estimations of serum electrolytes, urea and creatinine; full blood count, ESR, prothrombin time, thrombin time, and partial thromboplastin time; antistreptolysin-0 titre and antinuclear factor; serum IgA, IgG, IgM, C3 and C4 concentrations; and three 24-h urinary collections for estimation of creatinine clearance and proteinuria.

All patients with a history of macroscopic haematuria and those with one or more positive dipsticks were pursued to diagnosis. To this end all patients in these categories underwent intravenous urography and cystoscopy. Other investigations included renal ultrasound scan, DTPA renography, and renal angiography depending on clinical indications. Renal biopsy was performed in those patients in whom a cause for haematuria was not yet apparent. The only exceptions were those with exercise-induced haematuria and those over 50 years of age. In those with exercise haematuria alone who were otherwise asymptomatic with no significant proteinuria and without persistent haematuria, if cystoscopy and IVU were normal then renal biopsy was not performed. Similarly, renal biopsy was not performed in those patients over 50 with persistent haematuria and normal cystoscopy, IVU and renal function, and without proteinuria, but they were kept under review.

Results

One hundred patients entered the study and most completed the protocol. Ten patients were unable to complete all nine specimens, six were cystoscoped early to fit in with operating schedules, one was referred for urgent investigation of a mass discovered on his chest radiograph, and three were discharged early because of personal or service commitments. Data were incomplete on several urines due to lack of documentation on the ward or in the laboratory. Of a possible 900 results 825 were available for analysis.

1. Comparison of cell count with dipstick

Figure 1 and Table 1 show the comparison between red cell counts and reagent strip results using ward data. Urines giving a "haemolysed trace" result and those giving a "non-haemolysed trace" result are both included in the trace group. Twenty-four per cent of urines giving a negative dipstick result contained 10 or more RBC/μl; 11% contained 15 or more RBC/μl. The corresponding figures for a trace positive result are 82 and 62% respectively. Virtually all urines giving results of + or greater contained 10 or more RBC/μl.

In order to evaluate the usefulness of repeated dipstick testing in each patient, the patients were divided into three groups; those in whom dipstick testing was consistently negative (Group 1), those in whom one or more dipsticks were trace positive but no greater (Group 2), and those in whom any urine was more than trace positive (Group 3). The groups were compared by calculating the mean of the red cell counts for each patient. Figure 2 gives the results of these mean red cell counts (MRCCs) for patients in each group. In group 1, with 21 patients, the MRCC ranged from 0 to 3.9 RBC/μl. In this group only nine of the 180 urines tested contained more than 5 RBC/μl; eight contained 10 RBC/μl and one 20 RBC/μl. In group 2, with 27 patients, the MRCC ranged from 0 to 38 RBC/μl, with just five patients having MRCCs in the same range as patients in group 1. In group 3 the MRCC ranged from 5.5 to 500 RBC/μl. Two patients had MRCCs less than 10 RBC/μl; one of 5.5 and one of 9.5. The remainder had MRCCs of 14 or greater, with 85% of the 52 patients having MRCCs greater than 20 RBC/μl.

2. Correlation with pathology

All patients with positive dipsticks were found to have pathology to account for haematuria, with the exception of those with exercise haematuria and those aged 50 years or more. Patients in these last two categories were investigated as detailed above, investigations stopping short of renal biopsy unless there were other indications that a significant glomerulonephritis was present. The patients in group 2 are of special concern as it is the

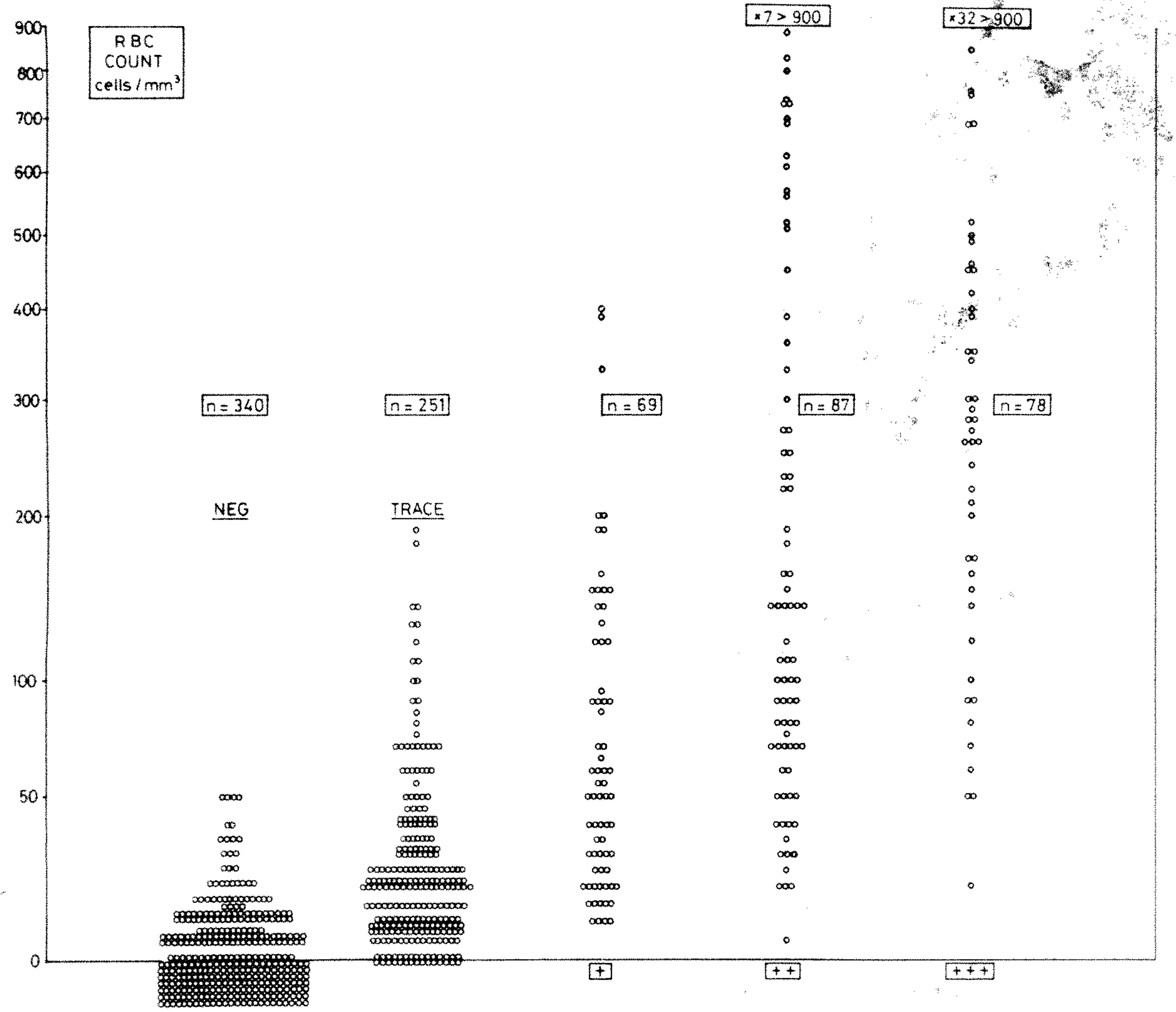

Fig. 1 Correlation of dipstick results with microscopy of the urine. Each circle represents one urine result, the vertical axis indicating the red cell count (RBC/μl) and the horizontal axis the dipstick result.

Table 1 For Each Reading of the Dipstick the Following are Shown: Number of Urines Containing ≤5 RBC/μl, ≥10 RBC/μl, and Percentage of Urines Containing ≥10 RBC/μl

N-Multistix-SG	*No of counts*		
Result	*≤5*	*≥10*	*%≥10*
Neg	257	83	24.4%
Trace	46	205	81.7%
+	0	69	100%
+ +	1	86	98.9%
+ + +	0	78	100%
Total	304	521	

significance of trace positive results that is usually questioned. Table 2 shows the final diagnoses for the 27 patients in group 2 with their age, sex, MRCCs, and number of trace positive dipsticks. Four patients had normal investigations, including IVU and cystoscopy, but renal biopsy was not performed. In three this was due to the patient's age, whilst the other patient had exercise haematuria with a single trace positive dipstick out of eight urines tested. A further patient was found to have an inflamed right ureteric orifice at cystoscopy. IVU and retrograde pyelography were normal, urines were sterile, and culture of early morning urines and urines from ureteric catheterisation were negative for *Mycobacterium tuberculosis*. The

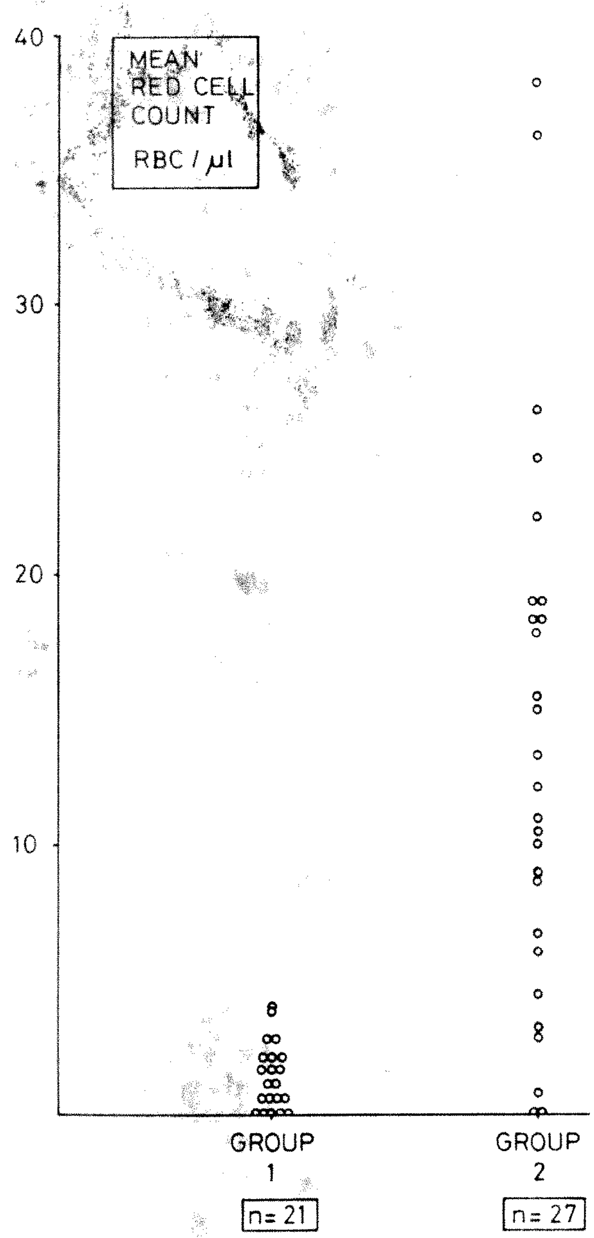

Fig. 2 Mean red cell counts (RBC/μl) are shown for patients in groups 1 and 2.

remaining 22 patients all had a well-defined source of bleeding from the urinary tract.

Table 2 Data on Patients with One or More Urines Giving a Dipstick Result of Trace Positive but no Greater (Group 2)

Age	*Sex*	*MRCC*	*No of positive dipsticks*	*Diagnosis*
59	M	0	2	No biopsy due to age
45	M	0	2	Cystitis
25	M	0.6	1/8	Exercise haematuria
35	M	2.8	7	Glomerulonephritis
18	M	3.3	1	Prostatitis
37	M	4.4	2	Glomerulonephritis
39	M	6	1/5	Urolithiasis
31	M	6.7	8	Glomerulonephritis
35	M	8.6	3/7	Glomerulonephritis
35	M	8.9	3	Hypospadias Urethritis
44	F	10	6	Cystitis
42	M	10.5	7	Glomerulonephritis
52	M	11	1/5	Right ureteric orifice inflamed
22	M	12.2	5	Glomerulonephritis
29	M	13.3	6	Glomerulonephritis
19	M	15	3	Trigonitis Glomerulonephritis
32	M	15.5	3	Urethral inflammation
20	M	17.8	6	Trigonitis
36	M	18.3	9	Urethral inflammation Glomerulonephritis
23	F	18.3	3/6	Cystitis
21	M	18.9	3	Urethral inflammation
19	M	18.9	9	Glomerulonephritis
40	M	22.2	2	Urolithiasis
49	M	24.4	3/8	No biopsy due to age
50	M	26.3	8/8	No biopsy due to age
38	M	36.4	7/7	Glomerulonephritis
34	M	38.3	8	Glomerulonephritis

Table 3 Comparison Between Results of Dipstick Testing on the Ward and in the Laboratory

		Laboratory Testing				
		Neg	*Trace*	+	+ +	+ + +
Ward Testing	*Neg*	229	99	5	—	—
	Trace	18	185	43	4	—
	+	—	17	39	7	4
	+ +	—	8	27	25	26
	+ + +	—	2	3	20	55

3. Comparison of dipstick testing on the ward and in the laboratory

Table 3 shows the comparison of dipstick testing in the laboratory and on the ward. Urines were more frequently scored as trace by the laboratory when negative on the ward than vice versa. Total agreement on scoring was reached in 65% of urines. A number of urines were reported as "very faint trace" or "? very faint trace" by the laboratory, whereas ward staff gave a clear decision on all urines as being either positive or negative. If these doubtful positives in the laboratory are scored as negative then there is no longer a bias towards positivity in the laboratory (Table 4), with agreement between laboratory and ward now 70%.

Table 4 Comparison Between Results of Dipstick Testing on the Ward and in the Laboratory, when Urines Recorded as Giving a Doubtful Positive Result in the Laboratory are Scored as Negative

		Laboratory Testing	
		Neg	*Trace*
Ward Testing	*Neg*	291	37
	Trace	45	158

The cell count in these doubtful positive urines ranged from 0 to 35 RBC/µl, with 41% of urines containing 10 or more RBC/µl and 20% containing 15 or more RBC/µl. Several of the 21 patients consistently negative on the ward had one or more doubtful positive results in the laboratory. Ward results were used as the "correct" dipstick result, as this is how it would occur in clinical practice.

Discussion

Whilst the importance of recognising significant haematuria has been stressed by many authors, the definition of significant haematuria remains vague. Addis (1926) found up to 425,000 red cells in the overnight urine of healthy people and suggested that up to 1 million red cells might be normal. The average overnight urinary volume was 352 ml, giving an upper limit of normal of 2 to 3 RBC/µl. His studies were done using bright light microscopy, which may miss a high proportion of red cells (Fairley and Birch, 1979; Fasset *et al.*, 1982; Kincaid-Smith, 1982). More recently, in a population survey using phase contrast microscopy, it has been suggested that the upper limit of normal is 8 RBC/µl (Fairley and Birch, 1982; Kincaid-Smith, 1982), a figure which compares well with Addis' figures using bright light microscopy. Such methods are reasonably accurate and reproducible, but also time-consuming and seldom used routinely. Microscopy of the urinary deposit is more common and is a routine in many laboratories. Methods vary and it is not surprising that the quoted upper limit of normal has ranged from less than 1 to 40 red cells per high power field (RBC/hpf) (Larcom and Carter, 1948; Wright, 1959; Freni *et al.*, 1977). Also it is our experience, and that of others (Freni *et al.*, 1977; Kesson *et al.*, 1978), that routine microscopy often misses low levels of significant haematuria. In short, microscopy of the urine proves either time-consuming or inaccurate in the detection of haematuria.

It is therefore not surprising that chemical tests have become popular and are now widely used, having the advantage of speed, convenience, and not being confined to the laboratory, whether ward-based or centralised. The test for blood on the N-Multistix-SG reagent strip, in common with other chemical tests, is based on the peroxidase-like activity of haemoglobin which catalyses the reaction of cumene hydroperoxide and 3,3′, 5,5′,-tetramethyl benzidine. Consequently the test detects intact red cells, free haemoglobin and myoglobin. Certain oxidising contaminants (such as hypochlorite) may lead to false positive results, whilst the presence of significant quantities of certain reducing agents (such as Vitamin C) may lead to false negative results.

Our results show that whilst there is a trend towards higher cell counts with greater positivity of the dipstick, the scatter of results is wide (Fig. 1). As in other studies of chemical tests (Smith *et al.*, 1977; Bee *et al.*, 1979), we find the N-Multistix-SG to be semiquantitative in assessing the degree of haematuria. More important is the ability of the test to predict the presence or absence of significant haematuria. For reasons given above there is good cause to accept the upper limit of normal for red cell counts using phase contrast microscopy as around 8 RBC/µl. As stated, the method we used for counting red cells limits reporting to multiples of 5 RBC/µl. We have therefore accepted 5 RBC/µl or less as being normal and 10 RBC/µl or more as abnormal. Taking this definition of significant haematuria, we have found that in our selected sample (*i.e.* patients known to have or suspected of having haematuria), 16% of urines associated with significant haematuria gave a negative dipstick result, 39% a trace positive result and 45% a result of greater positivity. Of those without significant haematuria, 85% gave a negative result, 15% a trace positive result and one urine specimen (0.3%) a result of greater positivity. Looked at from the point of view of the dipstick as a *predictor* of significant haematuria, we find a probability of 24% for a negative result, 82% for a trace positive result and 99% for a result of + or more.

By employing Bayes' theorem (Weinstein and

Fineberg, 1980; Strike, 1981) we could draw some inference upon the likely behaviour of the dipstick in an unselected population, but some difficulty arises here with regard to the status of our "non-haematuria" group. This group has been defined retrospectively (on the basis of observed cell counts) as a sub-set of an initially high-risk sample and as such it cannot be regarded as a random sample of non-haematuria subjects in the population at large. The status of our non-haematuria sub-group precludes any inference beyond the terms of our study, which was specifically restricted to observing the behaviour of the dipstick in suspected renal or urological disease referrals. This point is underlined by our experience of the dipstick in routine health screening of Royal Air Force personnel, which does not reflect the high proportion of false positive trace results (15%) observed in our "non-haematuria" sub-group.

More important than the simple correlation with red cell counts is the ability of the dipstick to predict the presence of pathological haematuria. In this study all patients with one or more positive dipsticks, even if only trace positive, were found to have pathology to account for their haematuria when pursued to a diagnosis. Exercise haematuria is a benign condition (Alyea and Parish, 1958; Siegel *et al.*, 1979; Kincaid-Smith, 1982) and in the absence of persistent haematuria or other pointers to a significant glomerulonephritis, renal biopsy was not performed. In the older patient we did not feel that renal biopsy was justified unless there were other factors, such as impaired renal function or proteinuria, suggesting that any underlying glomerulonephritis carried a poor prognosis. Some of the patients with only trace positive dipsticks had haematuria in the same range as those with consistently negative dipsticks as judged by the MRCCs. It may be that dipsticks pick up pathological haematuria missed by microscopy due to haemolysis. In one study of haematuria (Adams *et al.*, 1962) it was found that 90% of urines had evidence of haemolysed blood and in 70% of urines at least half of the blood present was haemolysed. The use of mean red cell counts is not conventional and to our knowledge no studies have been done to establish a normal range. Nonetheless we have found them to be useful in comparing several results from one patient with several results from another.

What of those patients with consistently negative dipstick results? Only nine urines (5%) of the 180 tested in this group of patients contained 10 or more RBC/µl. These nine urines came from seven patients. Two presented with exercise haematuria alone, one (a man of 66) was found to have benign prostatic hypertrophy, and four younger patients were not investigated invasively. It could be argued that significant pathology has been missed in these patients. However, if the upper limit for normal red cell counts is determined in a population survey, such that 95% of urines in a healthy population contain less than this number of red cells, one might expect about 5% of urines from normal individuals to contain "significant haematuria". Therefore none of these patients has been recalled for further tests and we feel that it would be unethical to subject them to invasive investigations without clinical or laboratory evidence of significant urinary tract pathology.

In our study the laboratory staff have read the dipstick with a more critical eye than the ward staff, which is perhaps to be expected in view of their different training, and this is reflected in the discrepancies between dipstick results in the laboratory and on the ward. Earlier studies with another dipstick showed that the sensitivity of the test could be improved by such critical reading and the use of a hand lens (Freni *et al.*, 1977). However, the test was not designed to be used in this way and recording such urines as positive increases the sensitivity of the dipstick at the expense of an increase in false positive results.

In summary, we have found the N-Multistix-SG test for haematuria to be a useful guide to the presence or absence of significant haematuria in those patients already suspected of having urinary tract pathology. Several specimens from each patient should be tested. Examination of the urinary deposit for other abnormalities remains an essential investigation in those patients suspected of having urinary tract pathology, and is best performed by the interested clinician on the ward using phase contrast microscopy. Phase contrast microscopy is essential to exclude red cells in the urine if a diagnosis of haemoglobinuria is suspected.

Further studies are needed to evaluate the performance of the dipstick as a screening test for haematuria in the general population. Nonetheless our findings would suggest that in this context a result of + or greater merits further investigation. If a trace positive result is obtained, repeat testing on several urines is indicated.

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The Authors

J. P. Arm, MA, MRCP, Senior Specialist in Medicine.
E. B. Peile, MRCP, MRCGP, General Practitioner.
D. J. Rainford, MBE, FRCP, Consultant in Renal Medicine.
P. W. Strike, MPhil, FSS, Statistician, RAF Institute of Pathology and Tropical Medicine.
R. E. Tettmar, MRCPath, Consultant Microbiologist, RAF Institute of Pathology and Tropical Medicine.

Requests for reprints to: Wing Commander D. J. Rainford, Department of Renal Medicine, PM RAF Hospital, Halton, Aylesbury HP22 5PG.

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Significance of Dipstick Haematuria. 2. Correlation with Pathology

J. P. ARM, E. B. PEILE and D. J. RAINFORD

Department of Renal Medicine, PM RAF Hospital, Aylesbury

Summary—In an evaluation of a chemical test for haematuria, all patients with positive results or a history of frank haematuria were investigated to determine the source of bleeding. In 10 of the 92 patients in whom the diagnosis was unknown at the time of admission, the presence of haematuria could not be confirmed. Of the remaining 82 patients urinary tract pathology was identified in 74. Of the other eight patients, four had exercise-induced haematuria with no other indications of significant pathology, and in four patients investigations stopped short of renal biopsy because of the patients' age.

Reagent strip testing of the urine is widely used in the detection of haematuria. It is our experience that many doctors consider these tests to be too sensitive and are reluctant to refer patients for investigation on the basis of a positive dipstick alone. It has also been suggested that asymptomatic microscopic haematuria in young adults is seldom associated with significant pathology and that full investigation is therefore not necessary (Froom *et al.*, 1984). We have studied a group of patients referred for investigation of haematuria to determine the correlation of the dipstick results with both microscopy of the urine and the presence of urinary tract pathology. The correlation with red cell counts of unspun urine is the subject of our preceding study (Arm *et al.*, 1986). All patients with one or more positive dipsticks were found to have urinary tract pathology when fully investigated. This report gives further details of the pathology found and its implications.

Patients and Methods

Details of patients and methods were given in our earlier report (Arm *et al.*, 1986) and only an outline will be presented here. Between January 1982 and June 1983 100 patients, referred for investigation of haematuria, were admitted to the study. Nine urines were collected from each patient and a comparison made between the results of dipstick testing on the ward and cell counts performed in the laboratory. The laboratory results were not known on the ward during the investigations. All patients with a definite history of frank haematuria and all patients with one or more positive dipstick results were investigated to determine the cause of their haematuria. In patients with exercise haematuria and in those aged 50 years and over, investigations did not include renal biopsy unless there were other indications of a significant glomerulonephritis.

Results

In eight of the 100 patients admitted to the study the diagnosis was known at the time of admission. Of the remaining 92 patients there were eight women (aged 20-62 years; average 33) and 84 men (aged 16-66 years; average 32). Thirty patients had presented with frank haematuria and 62 with microscopic haematuria. The disproportionate number of men and the young average age of the patients reflect the referral pattern of our unit, which deals mostly with service personnel. The final diagnoses are given in Table 1. Several

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Table 1 Final Diagnoses in the 92 Patients in whom the Diagnosis was Unknown at the Time of Admission

Women	
No haematuria	1
Loin pain haematuria syndrome	2
Urinary infection	3
Trigonitis	2
Total	8
Men	
a. Single Diagnosis	
No haematuria	9
Glomerulonephritis	32
Lower tract pathology	18
Benign prostatic hypertrophy	5
Exercise-induced haematuria	7
Urolithiasis	3
Primary carcinoma of bronchus	1
No renal biopsy (due to age)	4
b. More than one diagnosis	
Glomerulonephritis; urolithiasis	1
Glomerulonephritis; lower tract pathology	3
BPH, cystitis cystica	1
Total	84

patients had more than one pathology to account for their haematuria.

1. *Women*

Five of the eight women had inflammatory lesions of the lower urinary tract. Two of these women had cystitis with significant bacteriuria. One had had several episodes of cystitis, was currently asymptomatic with negative urine cultures, but had an inflamed bladder mucosa at cystoscopy. Two were asymptomatic with no previous history of cystitis and with negative urine cultures, but had trigonitis at cystoscopy.

Two women were thought to have loin pain haematuria syndrome on clinical grounds. In one the diagnosis was confirmed angiographically. In the other, angiography was of poor quality and renal biopsy was not performed. The symptoms of this latter patient settled when she stopped taking an oral contraceptive.

2. *Men*

Glomerulonephritis. The clinical and histological findings of patients with glomerulonephritis are summarised in Table 2. All patients had a focal or diffuse proliferative glomerulonephritis with or without expansion of the mesangium. Several patients had irreversible changes as judged by the presence of interstitial fibrosis, periglomerular fibrosis, or significant glomerular sclerosis. A variety of patterns of immunofluorescence was seen. All patients had normal renal function as measured by endogenous creatinine clearance.

Lower Urinary Tract Pathology. This group included patients with inflammatory and/or infective changes in the lower urinary tract, other than those with benign prostatic hypertrophy. The Figure shows their presentation and subsequent investigation. One patient was omitted because cystoscopy was technically unsatisfactory. He was asymptomatic, but of 10 MSUs one yielded significant bacteriuria and three grew mixed contaminants. Haematuria resolved when he was treated with antibiotics.

Two patients with IgA nephropathy were found to have trigonitis at cystoscopy. Neither had symptoms or a previous history of urinary infection and MSUs were sterile. Renal biopsies were performed because the histories were strongly suggestive of IgA nephropathy. A further patient was found to have inflammatory changes in the lower urinary tract which resolved on follow-up; persistent haematuria led to renal biopsy and a diagnosis of glomerulonephritis. In contrast, several patients with prostatitis, diagnosed on both clinical and laboratory evidence, had normal endoscopic examinations.

Two patients were found to have inflammatory changes at one ureteric orifice. In both patients IVU and retrograde pyelography were normal, and cultures of early morning urines and urines obtained from ureteric catheterisation were negative for *Mycobacterium tuberculosis*. Two patients had glandular hypospadias which had not been noted prior to referral; one had had recurrent urinary infections with frank haematuria, whilst the other presented with dipstick haematuria and was found to have an inflamed urethra at cystourethroscopy.

Exercise-induced Haematuria. Two patients referred for evaluation of exercise-induced haematuria had prostatitis, the diagnosis being made on clinical grounds and in the light of positive cultures. They are included in the Figure. The other five patients had presented with gross haematuria on one or more occasions after exercise and which had cleared rapidly. All were otherwise asymptomatic and none had persistent haematuria. In three patients cystoscopy was normal. One had prominent veins at the trigone and a urethral stricture,

Table 2 Findings in Patients with Glomerulonephritis

				Light microscopy					*Immunofluorescence*				
Age	*Prot G/l*	*H/T*	*IgA*	*Gloms*	*No. Scler*	*F/D*	*PGF*	*InF*	*IgA*	*IgG*	*IgM*	*C3*	*F*
31	<0.1	–	N	19	0	F	–	–	Inadequate tissue				
40	<0.1	–	N	10	0	D	–	–	–	–	–	+	–
35	<0.1	–	N	26	0	D	–		No tissue				
20	<0.1	–	N	50	0	F	–	–	+ +	+	+	+ +	+
28	<0.1	–	N	22	0	D	–	+/–	–	–	–	–	–
20	0.9	–	4.6	19	2	D	–	+	+	–	–	+	–
29	<0.1	–	N	30	2	F	–	–	+ +	–	+	+ +	–
23	0.8	+	4.6	20	1	D	+	+	–	–	+	+ +	+ + +
37	<0.1	–	N	32	0	D	–	–	–	–	–	–	–
22	<0.1	–	N	37	0	F	–	–	–	+	+	+	–
35	<0.1	–	N	8	0	D	–	–	–	–	–	+	+
27	0.7	–	N	28	0	F	–	–	–	+ +	–	+	+
22	<0.1	–	4.7	16	1	F	–	–	+ +	–	–	+ +	–
23	2 to 5	–	N	20	4	D	+/–	+ +	+	+	+	+	+
17	<0.1	–	N	7	0	D	–	–	–	–	–	–	–
22	<0.1	–	4.9	23	1	F	+	–	+	–	+	+ +	+
19	<0.1	–	N	20	0	F	–	–	–	–	+	+ +	+
30	<0.1	–	N	24	3	D	+/–	–	–	–	–	+	+
29	<0.1	–	N	24	0	D	–	–	–	–	–	–	+
36	<0.1	–	N	18	0	D	+/–	–	–	–	+	–	–
18	<0.1	–	N	17	0	F	–	–	–	–	+ +	–	–
45	0.7	+	N	20	2	D	–	–	–	–	+	–	–
42	<0.1	–	N	40	0	F	–	–	–	–	–	–	–
24	<0.1	–	N	18	0	D	–	–	+	–	–	–	+
38	<0.1	–	N	26	0	F	–	–	–	–	+	–	–
35	1.8	–	N	15	0	D	–	–	+	–	–	–	+
27	2.0	–	N	30	1	D	+/–	–	+ + +	–	+	+	–
25	<0.1	–	N	30	0	F	–	–	–	–	–	+	+
46	<0.1	–	N	36	0	F	+/–	–	+ +	–	+	+ +	+ +
23	0.8	–	N	19	0	D	+	–	+ +	–	–	+ +	+
25	1.0	–	N	14	0	F	–	–	+	–	+ +	–	+ +
45	<0.1	+	N	20	2	F	–	–	–	–	+	+	+
34	<0.1	–	N	25	0	D	–	–	+ +	–	+ +	+	–
19	<0.1	–	N	26	0	D	–	–	+ +	–	+	–	–
28	<0.1	–	N	55	0	F	+/–	–	–	–	+	+	–
26	<0.1	–	N	25	0	F	–	–	+ +	–	+ +	+ +	–

Details are given of proteinuria; presence or absence of hypertension; serum IgA (reference range 1.5-4.5 g/l); number of glomeruli (Gloms) available for light microscopy with number of sclerosed glomeruli (No Scler), whether the process was focal or diffuse (F/D) and the presence or absence of periglomerular fibrosis (PGF) and interstitial fibrosis (InF). Assessment of the degree of PGF and InF is given (+/– minimal, + definite, + + marked). Results of immunofluorescence to IgA, IgG, IgM, C3, and Fibrin (F) are given, scored from negative to + + +.

and the other was noted to bleed easily from trigone and prostatic urethra at cystoscopy.

No Haematuria. Nine men and one woman were referred for investigation of dipstick haematuria which could not be confirmed. In the absence of any other clinical or laboratory evidence of pathology, invasive investigations were not performed.

No Renal Biopsy Due to Age. Four patients aged 50 and over had persistent haematuria with normal cystoscopy and IVU. These patients may well have had glomerulonephritis, but in the absence of significant proteinuria or impairment of renal function renal biopsy was not performed.

Others. There were six patients with benign prostatic hypertrophy, one of whom was also noted to have cystitis cystica. Four patients had urolithiasis; one had proteinuria of 1 g/day and was found to have glomerulonephritis on renal biopsy, in addition to his urolithiasis. The patient with carcinoma of the bronchus presented with microscopic haematuria found at annual medical examination.

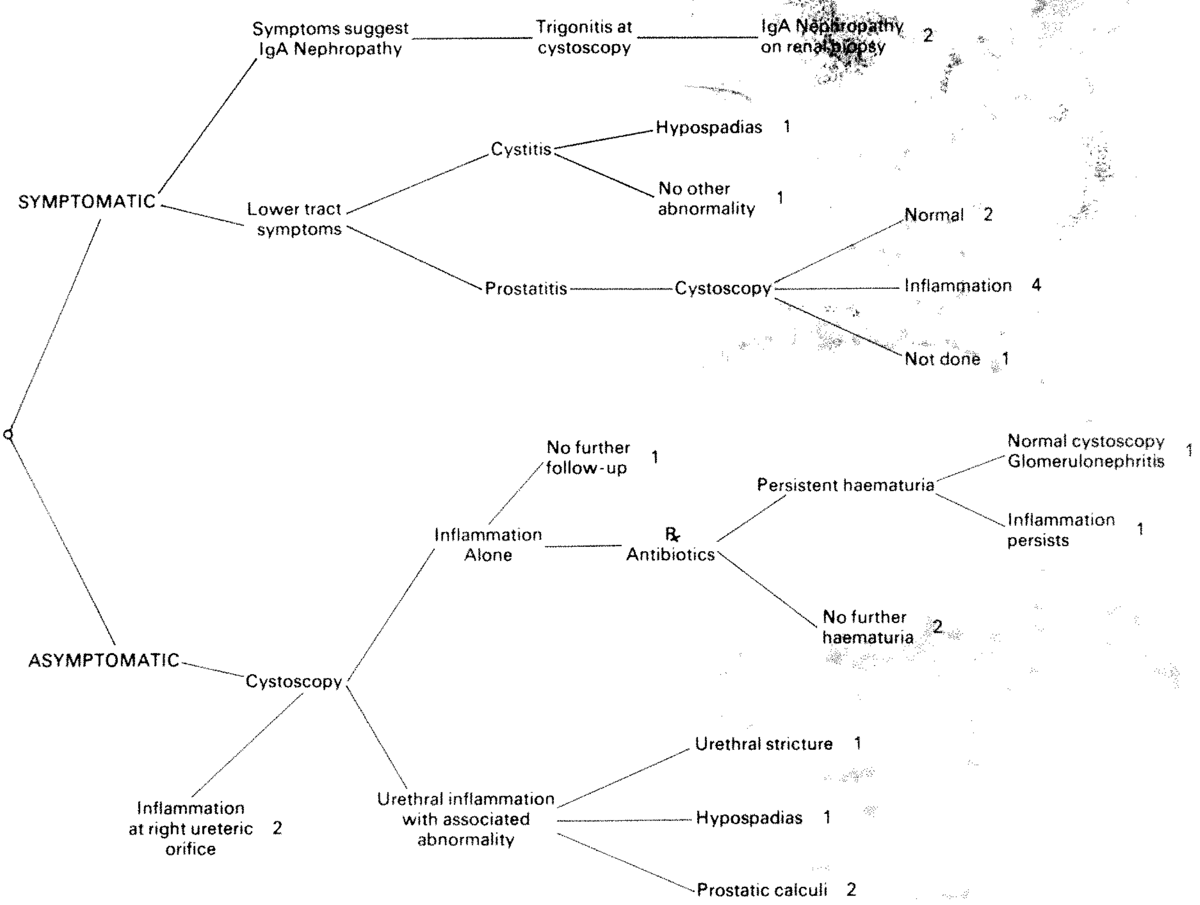

Fig. Investigations of 22 male patients with inflammation and/or infection of lower urinary tract. Figures refer to numbers of patients.

The diagnosis was made on routine chest radiography during investigation of his haematuria. IVU was normal and no other primary was found. Histology of the resected lung suggested that the carcinoma was a lung primary.

Discussion

In an earlier retrospective study of asymptomatic microscopic haematuria, Greene *et al.*, (1956) found that a diagnosis was reached in only 56% of cases. Twenty-three years later a report from the same centre (Carson *et al.*, 1979) showed that a diagnosis was now reached in 81% of cases. The increased diagnostic success was attributed to superior diagnostic techniques (Carson *et al.*, 1979; Greene, 1980). The investigations in both series had a urological bias with no diagnosis of glomerulonephritis in the first series and seven cases of "renal parenchymal disease" in the second. Others have found that most adult patients in whom haematuria remains undiagnosed after careful urological assessment are found to have glomerular disease at renal biopsy (Burkholder *et al.*, 1969; Chen *et al.*, 1972; Hendler *et al.*, 1972; Van de Putte *et al.*, 1974; Kupor *et al.*, 1975; Michael *et al.*, 1976; Sinniah *et al.*, 1976; Pardo *et al.*, 1979). One would therefore expect a combination of rigorous clinical assessment and intelligent use of modern diagnostic techniques to result in a diagnosis in the majority of patients with haematuria. This is supported by Burkholder's series (Burkholder *et al.*, 1969) and our own results.

The commonest diagnosis amongst our patients was glomerulonephritis. As in other studies, most patients had mesangial proliferative nephritis, but several had evidence of progressive disease with irreversible changes. The literature suggests that the presence of haematuria with minimal or insignificant proteinuria indicates a good prognosis, at least in the short term (Labovitz *et al.*, 1972; Van de Putte *et al.*, 1974; Brown *et al.*, 1979; Pardo *et al.*, 1979), whilst proteinuria correlates with both progression of disease and severity of histological change (Hendler *et al.*, 1972; Alexander *et al.*, 1973; Van de Putte *et al.*, 1974). There are, however, both in this series and in others (Hendler *et al.*, 1972; Kupor *et al.*, 1975), some patients with haematuria alone in whom histological appearances are not so benign. The final outcome in these patients will only be apparent after careful long-term follow-up. It is notable that in two of the nine patients with significant proteinuria this finding had not been noted prior to referral.

The group of patients with lower tract pathology illustrates some important points and raises some important questions. The value of a careful history and examination has been stressed by Burkholder *et al.* (1969) and is well illustrated here. In several patients a diagnosis was suggested by history alone, and both cases of hypospadias were undiagnosed prior to referral. Examination of the patient with haematuria must include the genitalia, and also a rectal examination of the prostate for evidence of prostatitis or malignancy. It is important that urethroscopy precedes cystoscopy to avoid confusion between iatrogenic changes in the urethra and genuine pathology (Burkholder *et al.*, 1969). We had several patients, referred for renal biopsy, in whom previous cystoscopy had been reported as normal but had not been accompanied by prior urethroscopy. The significance of inflammatory changes is not always clear. When symptoms and cultures reveal the presence of infection their significance is apparent, but it is notable that urethroscopy may be normal in the presence of prostatitis. Furthermore, two patients with mesangial IgA disease had trigonitis at cystoscopy and in another patient, with asymptomatic microscopic haematuria, urethral abnormalities resolved whilst haematuria persisted, leading to a diagnosis of glomerulonephritis. Whilst it is tempting to attribute haematuria to mild inflammatory changes noted at cystourethroscopy it may be, especially in the asymptomatic patient with negative cultures, that haematuria is due to concurrent glomerulonephritis. A test that reliably distinguishes glomerular from non-glomerular bleeding would be useful. Fairley and Birch (1982) have described one such method based on glomerular morphology, and both they and others have reported good results (Fasset *et al.*, 1982). However, patients with mesangial IgA disease and those with coexisting glomerular and non-glomerular pathology often have a mixed picture of both normal and dysmorphic red cells (Fasset *et al.*, 1982). This may explain why we have had little success using this method to determine the source of bleeding in our patients.

Of the seven patients with exercise haematuria, two had prostatitis and a third had a urethral stricture. It is generally agreed that exercise haematuria which resolves in 24 to 48 h, in an otherwise normal individual, is an entirely benign condition (Kincaid-Smith, 1982). We agree, but would emphasise that exercise haematuria may be indicative of urinary tract pathology (*e.g.* glomerulonephritis, stones, urethral stricture). Exercise haematuria can only confidently be said to be benign after careful clinical assessment and in the absence of persistent haematuria.

Previous studies of haematuria have revealed an incidence of urinary tract malignancy of around 10% (Burkholder *et al.*, 1969; Carson *et al.*, 1979; Golin and Howard, 1980). These studies have been in older patients. The absence of such pathology in our series and the relatively large number of cases of glomerulonephritis reflect the average age of our patients. The only case of malignancy was a patient with bronchial carcinoma. It is possible that a renal primary was present that was too small to show up on IVU, or that lower urinary tract pathology was missed as cystoscopy was not performed. However, the association between malignancy and glomerulonephritis is well documented and this is another possible explanation for this man's haematuria.

A study from the Israeli Air Force recently suggested that microscopic haematuria is a common finding at routine medical examinations, but is rarely associated with significant pathology (Froom *et al.*, 1984). It was suggested that screening for haematuria in asymptomatic young men was not worthwhile, since positive results do not justify further work-up or treatment. However, haematuria was sought by microscopy of the urinary deposit and no clear definition of significant haematuria was available. Few patients were fully investigated and the average period of follow-up was only 7 years. It is difficult to compare the results of our own study in that a third of our patients presented with frank haematuria, several patients with microscopic haematuria had proteinuria too, and our patients had already been referred to hospital. However, our study was prospective, and all patients had a thorough work-up from a careful clinical assessment to rigorous application of modern techniques. A diagnosis was reached in all patients who were fully investigated for persistent microscopic haematuria. The pathology found was seldom trivial, and in several cases significant adverse features were present.

We therefore recommend that dipstick haematuria demands careful assessment. A full clinical assessment will often reveal unsuspected abnormalities and should include urine analysis for protein. Examination of the urinary deposit is of little value in confirming the presence of significant haematuria but may help in distinguishing glomerular from non-glomerular bleeding. If haematuria is persistent, a rigorous approach will almost always lead to a diagnosis. The significance of pathology discovered can only be known after careful long-term follow-up.

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The Authors

J. P. Arm, MA, MRCP, Senior Specialist in Medicine.
E. B. Peile, MRCP, MRCGP, General Practitioner.
D. J. Rainford, MBE, FRCP, Consultant in Renal Medicine.

Requests for reprints to: Wing Commander D. J. Rainford, Department of Renal Medicine, PM RAF Hospital, Halton, Aylesbury HP22 5PG.

British Journal of Urology (1986), **58**, 224-233

Case Reports

Bilateral Ureteric Obstruction due to Endometriosis Presenting with Hypertension and Cyclical Oliguria

R. W. GOURDIE and A. C. N. ROGERS, *Department of Urology, Royal Infirmary, Stirling*

Case Report

A 40-year-old woman was admitted with hypertension, treated by thiazides and discharged. She presented 1 month later with a 3-day history of oliguria and puffiness of face and ankles. Her blood pressure was 210/115, urea 26.9 and creatinine 1250. She became polyuric and there was sterile pyuria. She had noted passing less urine during the menses, which were regular, heavy but pain-free.

Intravenous urography showed only faint nephrograms; the right kidney was normal but the left was enlarged with a negative urogram. Cystoscopic appearances were normal. Ureteric catheterisation was blocked at 3 cm on the right and a stiff resistance was encountered at 6 cm on the left. Vaginal examination disclosed a 2-cm mobile nodule in the posterior vaginal fornix suggestive of endometriosis and confirmed by biopsy. The ureters were explored extraperitoneally and structures of 2 cm found at the true pelvic brim. No other lesions were discovered. Continuity was restored by primary anastomosis on the left and by Boari flap on the right. Histology showed intrinsic endometriosis of the ureteric wall. The menses were suppressed by danazol and later by radiation menopause. Post-operative urograms showed satisfactory drainage but there was post-obstructive atrophy of the right kidney.

Comment

This condition has been adequately documented by Abeshouse and Abeshouse (1960) and Ball and Platt (1962) but reports of bilateral involvement without associated intra-abdominal lesions are rare.

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Requests for reprints to: R. W. Gourdie, Department of Urology, Stirling Royal Infirmary, Livilands, Stirling FK8 2AU.

Penile Hyperexcitability as the Presenting Symptom of Rabies

M. BHANDARI and SANTOSH KUMAR, *Department of Urology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India*

Case Report

A 56-year-old man complained of hypersensitivity of the penis, in the form of erection and ejaculation at the slightest touch, together with dysuria, frequency and pain over the perineum, lower back and right thigh. There was no history of previous urogenital symptoms.

External examination was unremarkable. On rectal examination the prostate was moderately enlarged and tender and prostatic palpation elicited an erection with ejaculation. The patient was admitted with a provisional diagnosis of acute prostatitis. Routine blood and urine investigations were normal. Over the next 12 h the patient became increasingly apprehensive and excitable and had difficulty in swallowing. On enquiry, he admitted to having been bitten on the right thigh, 1 month earlier, by a pet dog which had been behaving abnormally and which he later killed. Our suspicion of rabies was confirmed by the physician. The patient was transferred to the Infectious Diseases Hospital and on the following day he exhibited hydrophobia and other features of central nervous system hyperexcitability; he died in coma 48 h after we first saw him. A post mortem was refused.

Comment

Priapism and spontaneous ejaculation, ascribed to the involvement of the amygdaloid nucleus in the brain, have been reported in the late stages of rabies (Corey, 1980). Penile hyperexcitability, without actual priapism, as the first sole manifestation of rabies is a unique feature of our case. The early predominant involvement of pudendal, sacral parasympathetic and lumbothoracic sympathetic nerves by the rabies virus, from the portal on the thigh, could account for the hyperexcitable neural arcs of erection and ejaculation.

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Requests for reprints to: M. Bhandari, Department of Urology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry—605006, India.

Primary Oat Cell Carcinoma of the Urinary Bladder

M. R. WILLIAMS, M. DUNN and I. D. ANSELL,
Departments of Surgery, Urology and Pathology, City and University Hospitals, Nottingham

Case Report

A 69-year-old man presented with terminal haematuria. Physical examination showed no abnormality apart from mild hypertension. Blood tests were normal and urine microscopy confirmed haematuria. An intravenous urogram showed a large filling defect in the dome of the bladder with no abnormality of the upper urinary tract. The chest X-ray was unremarkable.

At cystoscopy a large solid tumour was found infiltrating the vault and posterior wall of the bladder. Bimanual examination showed this to be a T3a tumour. The tumour was biopsied and histology showed extensive and deep invasion of the bladder muscle by a small cell undifferentiated carcinoma with appearances similar to those seen in oat cell carcinoma of the bronchus (Fig. 1). Because of the extensive invasion and histological grade a total cystectomy and ileal loop diversion were carried out.

The operative specimen consisted of bladder and prostate containing a solid white tumour 5 × 5 cm invading through the posterior wall of the bladder. Microscopically the tumour was an anaplastic carcinoma identical to that seen in the biopsy specimen. Electron microscopic examination showed membrane-bound neurosecretory granules in the tumour cell (Fig. 2). The macroscopic appearance and presence of an *in situ* carcinomatous change in neighbouring urothelium indicated that this was almost certainly a primary bladder tumour. The similarity between some small cell anaplastic bladder cancers and oat cell carcinoma of bronchus has been noted previously (Koss, 1975), although there is only one other report of the demonstration of neurosecretory granules in this type of bladder tumour (Cramer *et al.*, 1981).

Six months post-operatively he was admitted as an emergency with malaise, vomiting and severe dehydration. An intravenous urogram showed bilateral hydronephrosis and ureteric dilatation down to the level of the uretero-ileal anastomoses. At laparotomy the ureters were surrounded by dense fibrous tissue which was biopsied. Reimplantation of the right ureter and freeing of the left ureter were performed. No histological or gross evidence of residual or metastatic tumour was found and he made a full recovery.

Comment

Although histologically similar, the clinical behaviour of this tumour differs markedly from that of oat cell carcinoma of the lung, apparently running a more benign course. After a 2-year follow-up our patient is still well with no sign of recurrence.

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Requests for reprints to: M. R. Williams, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB.

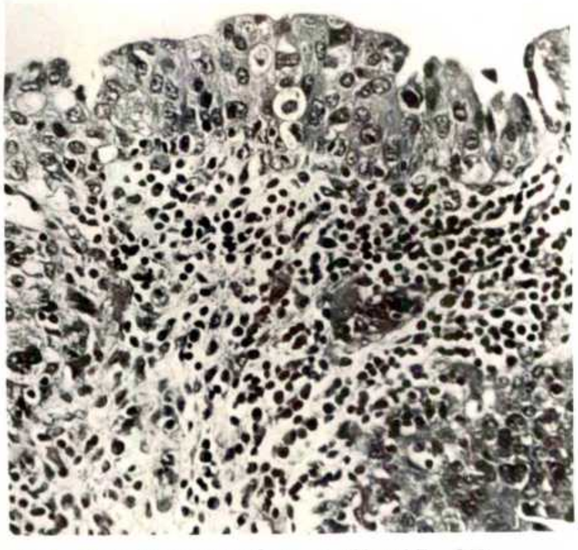

Fig. 1 Light microscopy of tumour. (H and E × 360).

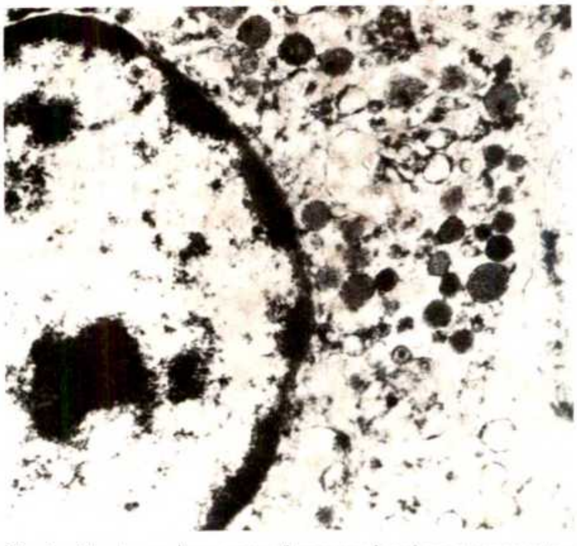

Fig. 2 Electron microscopy of tumour showing neurosecretory granules. (× 10,000).

The G-suit in Controlling Massive Urological Haemorrhage

D. W. RYAN, A. K. PRIDIE, P. JOHNSTON, P. H. POWELL and W. K. YEATES, *Department of Urology, Freeman Hospital, Newcastle upon Tyne*

Massive bleeding is a rare complication of transurethral prostatectomy. A case is presented in which the outlook appeared hopeless but haemorrhage was arrested by application of an anti-gravity suit (G-suit).

Case Report

An 80-year-old man with polymyalgia rheumatica underwent transurethral prostatic resection under spinal anaesthesia. At operation, grade IV prostatic obstruction with trilobar enlargement and intravesicular projection was noted. Following resection with acceptable haemostasis, the patient was transferred with irrigation to the recovery area. One hour later he was returned to the theatre as severe bleeding had developed. Under general anaesthesia the operation site was re-examined; a moderate amount of clot was evacuated from the bladder and a few bleeding vessels from the prostatic bed were diathermied, but severe bleeding persisted. The bladder was opened, some residual tissue was enucleated, haemostatic sutures were inserted, the site was packed with gauze and traction to the Foley catheter applied. The bleeding continued and the patient was transferred to ITU in a shocked condition for ventilation and further resuscitation. Large supportive transfusions of blood, clear fluids and clotting factors were commenced. Digital compression of the operative site *per rectum* was tried without avail; an infusion of epsilon aminocaproic acid into the bladder was tried without success.

During this phase vasoconstriction occurred with a rise in blood pressure from 80 to 160 mmHg, the pulse rose to 140 beats per min and the cardiovascular pressure fell to -8 cmH$_2$O. Analgesia and sedation were given in an attempt to reduce the blood pressure, which might aggravate bleeding. The patient was finally placed in a G-suit, covered by towels to protect the skin, and the suit inflated to 30 mmHg. Haemorrhage was reduced almost instantly, although the irrigation was unaffected: resuscitation continued satisfactorily with the patient receiving in this 2-h period 11 units of blood, 6 packs of fresh frozen plasma, 2 litres of clear fluids and 1500 ml of Haemocell.

Treatment in the G-suit continued on the following day, with deflation 10 min in every hour until 36 h post-operatively. The pack was removed on the following day: one small episode of clot retention occurred; otherwise the patient's condition remained stable and he returned to the ward 3 days post-operatively, with a good urine output.

Comment

The G-suit has applications in aviation medicine and in preventing postural hypotension in neurosurgical work as well as in resuscitation. Its use in Vietnam (Cutler and Daggett, 1971) for military injury and evacuation and in civilian practice as military antishock trousers (MAST) has endorsed its use in massive haemorrhage, trauma, pelvic and long bone injuries. Abernathy *et al.* (1979) considered it worth a two-unit autotransfusion as well as controlling or stopping intra-abdominal haemorrhage and stabilising fractures of the pelvis and long bones. In this country the G-suit has been used to control leaking aortic aneurysms and altered coagulation states (Lewis *et al.*, 1973). One previous case of prostatic haemorrhage in which disseminated intravascular coagulation developed (McCullough *et al.*, 1975) was successfully controlled following surgery.

The response to the suit is often dramatic, as in our case, providing a remarkably consistent improvement in a patient's haemodynamic state, often of a life-saving nature. It clearly is a holding-therapy to buy time rather than a definitive cure. Nevertheless, it is no less valuable in these trying circumstances. Respiration can become embarrassed unless artificially supported and skin damage occurs unless protective towelling is used.

The mechanism of action is unclear. The improvement in arterial pressure far exceeds the counter-pressure applied. It provides a useful venous return by mobilising a reservoir of blood from the area being compressed; the pressure compressing the lower abdomen and limbs will also tend to control haemorrhage by reducing the calibre of small lacerated vessels and tamponade of open arteries, but its ability to control hypocoagulation states, presumably by compression, is less well understood (Lewis *et al.*, 1973).

Our experience suggests that the G-suit has a role to play in the rare situation of severe haemorrhage after prostatectomy which persists in spite of conventional attempts to arrest it.

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Requests for reprints to: D. W. Ryan, Department of Anaesthesia, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN.

Renal Carcinoma Metastasis in Salivary Gland

D. WILSON STOREY and B. McGOWAN, *Department of Surgery, Barnsley District General Hospital, Barnsley*

A case of metastatic renal carcinoma presenting as an enlargement of the submandibular salivary gland is presented.

Case Report

A 60-year-old-male presented with a 2-year history of a painless, progressively enlarging swelling in the left submandibular region. He was otherwise well with no urinary symptoms. The left submandibular gland was subsequently excised, revealing a small, yellow, encapsulated tumour within the glandular tissue which light and electron microscopy suggested was a metastatic deposit from a renal carcinoma (Fig.). Intravenous urography and ultrasound scan revealed a solid lesion in the upper pole of the right kidney which showed a florid malignant circulation on renal angiography. A right nephrectomy was performed. Cross sections showed a yellow, circumscribed tumour 6.5 × 6.3 × 5.0 cm within the renal substance invading perinephric fat but not the renal vein. Histologically this was a renal carcinoma with histology comparable to that of the nodule within the salivary gland.

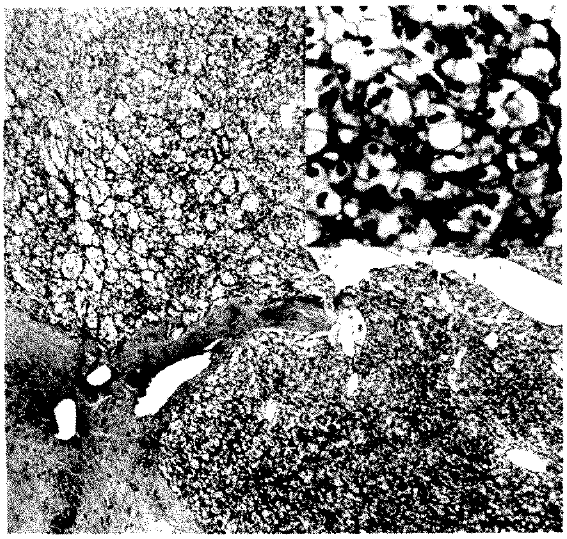

Fig. Renal carcinoma metastasis in submandibular salivary gland (× 140). (Insert × 620).

Comment

Renal carcinoma usually presents with either haematuria (62%), loin pain (50%) or a palpable abdominal mass (34%), with only 11% showing all three features (Riches *et al.*, 1951). The tumour metastasises via the bloodstream and/or lymphatics. Between 7 and 25% of patients present with signs and/or symptoms due to secondary deposits from a silent primary renal carcinoma (Skinner *et al.*, 1971). These include persistent cough or haemoptysis, spontaneous pathological fracture or, as in this case, a palpable swelling distant from the site of the primary disease. Apparently solitary metastases have been described in most organs of the body (Saitoh, 1981) but we believe that they have not previously been described in salivary tissue.

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Requests for reprints to: D. Wilson Storey, Department of Surgery, Barnsley District General Hospital, Gawber Road, Barnsley S75 2EP.

Prazosin, Priapism and Managment

A. V. KAISARY and P. J. B. SMITH, *Departments of Urology, Charing Cross Hospital, London and Royal Infirmary, Bristol*

Two patients were reported to develop priapism (persistent painful erection of the penis) while they were receiving prazosin treatment for hypertension (Bhalla *et al.*, 1979). We report two more cases and stress that priapism ought to be managed as a surgical emergency irrespective of the cause.

Case Reports

Case 1 A 49-year-old white man attended the Accident and Emergency Department complaining of persistent painful erection of the penis for 16 h. He was receiving prazosin and methyldopa at doses of 6 mg and 250 mg respectively daily for hypertension. Antihypertensive treatment had started 9 months earlier. He stated that he had experienced an attack of painful spontaneous erection lasting up to 1 h 6 weeks earlier.

He had no history of genitourinary disease and physical examination was unremarkable. Routine blood tests and clotting studies were normal. Sickle cell screening test was negative. An emergency saphenocavernous bypass and spongiocavernous anastomosis was performed. The corpora cavernosum tissues were biopsied. The penile engorgement disappeared over a period of 9 h. Prasozin treatment was stopped. Histological examination of the cavernous tissue showed normal lining of the vascular erectile tissue spaces. He was followed up for 3 years, during which time he had no further attacks of priapism and maintained his potency.

Case 2 A 56-year-old Jamaican was receiving methyldopa and prasozin for hypertension. Methyldopa was stopped following the development of impotence, after which he regained his potency. Clinical examination was unremarkable apart from a mild degree of cardiomegaly. Routine blood tests and coagulation studies were normal. Sickle cell screening test was negative. He experienced two attacks of painful erection that persisted for 2 and 4 days respectively, after which they resolved spontaneously. He developed a third attack 8 months after starting prazosin. The attack persisted for 2 days, after which he was referred to the urologists. Bilateral cavernosal spongiosal fistulae were created. Histological examination of the cavernous tissue biopsy showed an increased amount of hyaline fibrous tissue and vascular tissue containing smooth muscle bundles. He now has erectile impotence. He experiences normal glans sensation, orgasm and ejaculation.

Comment

Proper sexual function is known to depend on the integrity and co-ordination of the autonomic and somatic nervous systems. Erection and ejaculation proper are parasympathetic effects, while emission is a sympathetic one (Silverstein, 1980). Hypothalamic stimuli along the sacral parasympathetic outflow will lead to an adjustment of the blood flow in the penile erectile tissue. The arterial blood will enter the erectile spaces of the corpora cavernosa and spongiosum and erection is produced (Conti, 1952). Prazosin, an antihypertensive agent, is thought to interfere with α-adrenoceptor function at the post-synaptic level (Graham and Pettinger, 1979). This seems to encourage parasympathetic dominance. Two West Indian patients were reported to have had recurrent attacks of priapism while being treated with prazosin for hypertension (Bhalla *et al.*, 1979). We present two more cases to emphasise that priapism is a potential hazard of treatment with prazosin.

Hinman (1960) explained that various treatments offered for priapism fail when they do not restore venous drainage early enough to eliminate the damage to the local erectile mechanism, so that speedy recognition, referral and treatment are the factors that determine whether the patient stands a chance of retaining his potency. How (1969) stated that priapism is a urological emergency.

Acknowledgements

We thank Mr P. F. Philip, Consultant Urologist at Charing Cross Hospital, and Dr D. W. Barritt, Consultant Physician at Bristol Royal Infirmary, for permission to report these cases.

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Requests for reprints to: A. V. Kaisary, Department of Urology, The Churchill Hospital, Headington, Oxford, OX3 7LJ.

Pyeloduodenal Fistula

A. R. A. ABDALLA and A. IBRAHIM, *Department of Surgery, University of Khartoum, Sudan*

Case Report

A 21-year-old female presented with a 3-year history of right loin pain, fever and anorexia. Two months before admission she developed a swelling in the right loin, dysuria and bloody diarrhoea.

Examination revealed a pale woman with a temperature of 38.8 C and a palpable right kidney. Investigations were as follows: Hb 9.2 g/dl, WBC 8.9×10 g/l and ESR 110 mm/h. Biochemical studies were normal. The urine contained numerous pus cells with a heavy growth

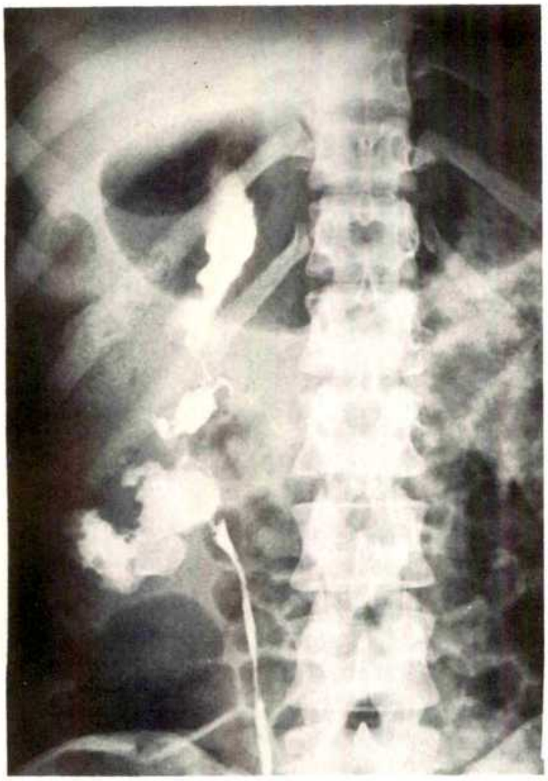

Fig. Right retrograde urography showing dilated pelvicaliceal system with free flow of contrast medium into the duodenum.

of *Escherichia coli* on culture. IVU showed a non-functioning right kidney and a pelvic stone. Cystoscopy revealed a markedly inflamed bladder from which offensive urine was drained. Right retrograde urography showed a dilated pelvicaliceal system with free flow of contrast medium into the duodenum (Fig.).

Right nephrectomy was performed with division and repair of the fistula in the duodenum.

Comment

Almost all cases of pyeloduodenal fistula have occurred on the right side. A spontaneous pyeloduodenal fistula usually originates in the kidney and may occasionally complicate duodenal ulceration.

Chronic renal infection associated with obstruction accounts for most cases. Of the 32 cases reported in the literature, 24 were due to chronic infection; 15 of these had a calculus and 10 also had a perinephric abscess. Five were tuberculous, two followed renal carcinoma and one patient had hydatid disease. Bissada *et al.* (1973) reported a rising incidence of associated calculus disease since 1945 and considered obstruction to be an important factor as well as infection. Patients with pyeloduodenal fistulas usually present with gastrointestinal symptoms. IVU often reveals a non-functioning kidney. The diagnosis is usually established by retrograde urography or, occasionally, by upper gastrointestinal barium studies.

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Requests for reprints to: A. R. A. Abdalla, Department of Surgery, Faculty of Medicine, P.O. Box 102, Khartoum, Sudan.

Chronic Retention after Extratrigonal Phenol Injection for Bladder Instability

R. COX and P. H. L. WORTH, *Department of Urodynamics, Shaftesbury Hospital and Institute of Urology, London*

The extratrigonal injection of phenol is an established and successful treatment for bladder instability resistant to drugs. It has been reported to be free of serious complications (Blackford *et al.*, 1984). We report the development of chronic retention following a phenol injection.

Case Report

A 71-year-old female complained of frequency, urgency and incontinence. Videocystometry demonstrated phasic bladder instability with a maximum subtracted detrusor pressure of 45 cm H_2O and urge and stress incontinence. A left nephrectomy had been performed for calculous disease 30 years earlier and a number of asymptomatic calculi were present in the lower pole of the remaining kidney. Serum creatinine was 0.26 to 0.28 mmol/l. The patient was unable to tolerate oxybutynin in a dosage adequate to improve her symptoms and so two injections of 10 ml of 6% phenol were placed as described by Blackford *et al.* (1984). The bladder was drained with a urethral catheter which was removed the next morning, after which the patient was unable to void. A further trial without catheter was unsuccessful and so a suprapubic catheter was inserted. One week after the phenol injection the urethra was dilated to 30 F but the patient remained incapable of voiding. Cystometry 12 days after injection showed the end filling pressure to be 40 cm H_2O achieved by a steady rise with no phasic contractions. Three months later the situation remained unchanged.

Comment

The injection of phenol to treat the unstable bladder was first described by Ewing *et al.* (1982). Of their 30 patients, five developed chronic retention and were reported to be happy with this situation, resorting to self-catheterisation. One hundred and sixteen patients were similarly treated by Blackford *et al.* (1984) and no patient developed chronic retention. Our patient is interesting in that she remained unstable but became unable to initiate a voluntary detrusor contraction; we hope the situation will improve with time.

The risk of developing chronic retention should be considered when advising phenol injection for an unstable bladder. The true incidence of this complication has yet to be established.

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Requests for reprints to: R. Cox, St Paul's Hospital, Endell Street, London WC2H 9AE.

Brushite Lithiasis of Prostate

A. S. GAWANDE, *Department of Urology, O'Bleness Memorial Hospital, Athens, USA*

This is the second reported case of brushite stone formation in the bed of a resected prostate causing repeated urinary retention.

Case Report

A 75-year-old white male was admitted with acute urinary retention. Cystoscopy revealed total occlusion of the prostatic fossa by hard yellow stones weighing from 1 to 8 mg. When scraped, the stones felt as if they were actually secreted by prostatic acini; it was virtually impossible to remove them all, but 2340 mg were removed. Crystallographic examination revealed brushite crystals deposited over hydroxy apatite. The patient had had four previous episodes of urinary retention and each time his prostatic fossa was filled with micro-calculi.

Comment

Prostatic calculi may be divided into two groups: endogenous or primary, where stones are formed inside the acinus mainly from prostatic fluids, and exogenous or secondary, where calculi are formed in the urethra or some existing pocket in the prostate and are derived from urine. Primary stones are composed mainly of apatite and whitlockite. Sutor and Wooley (1974) have shown that only these substances can be precipitated from the prostatic secretion.

It is postulated that primary prostatic calculi are formed in the bed of the enucleated prostate or after transurethreal prostatic resection, possibly due to devitalised residual tissue, acute or chronic infection, which act like a nidus for the precipitation of stone-forming elements. It is also possible that after transurethral resection of the prostate the mucoprotein produced by the prostatic glands acts like a nidus.

The pH of prostatic secretion is 6.35 to 6.65 and at this pH hydroxy apatite is formed. When it is exposed to acidic urinary flow (pH 6.2 or lower), brushite encrustations are formed in the prostatic bed. This particular patient had five distinct episodes of urinary retention due to prostatic encrustations. During his last episode of urinary retention, 2340 mg of calculi were removed; they were composed of 44% brushite, 35% hydroxy apatite and 17% monohydrate.

Brushite prostatic encrustations and lithiasis are uncommon. This is the second reported case of brushite prostatic stone. Magura *et al.* (1980) postulated that brushite calculi are caused by acidic urine, and so it may be possible to prevent or delay the process of stone formation in the prostatic tissue by alkalinisation of the urine. This has been done in this patient and he has had no stones for the last 14 months. As in Magura's case, there was brushite deposition over hydroxy apatite, thus supporting the theory that acidic urine rather than prostatic secretion created favourable conditions for brushite stone formation. It is also suggested that crystallographic analysis of prostatic stones may help in the management of prostatic calculus disease.

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Retroperitoneal Fibrosis with Azotaemia Secondary to Metastatic Breast Cancer

V. SRINIVAS and D. DOW, *Department of Surgery (Urology), Memorial University of Newfoundland, Health Sciences Center, St John's, Canada*

Retroperitoneal fibrosis secondary to metastatic breast cancer is a rare phenomenon (Carloss and Saab, 1980) and can occasionally result in acute renal failure.

Case Report

A 66-year-old female underwent a left radical mastectomy in 1977 for a stage II carcinoma of the breast. In February 1980 she developed metastatic lymph nodes in the neck and was treated initially with hormones (stilboestrol) followed by local radiotherapy (4000 rads) and systemic chemotherapy (cyclophosphamide). She was apparently well until February 1981, when she was readmitted with a 4-week history of malaise, lethargy and weakness. On admission her serum creatinine was 3.0 mg%; within 48 h this rose to 10.8 mg% and her urine output dropped to below 200 ml/24 h. Emergency haemodialysis brought the serum creatinine down to 5.7 mg%. A retrograde pyelogram revealed ureteric obstruction over the sacroiliac joint (Fig.) with a proximally dilated ureter and hydronephrosis. Bilateral retrograde ureteric catheters (No. 5F) were passed easily under local anaesthesia and a hydronephrotic urine drip was obtained. The serum creatinine fell rapidly to 1.7 mg% within 48 h and the urine remained uninfected. The catheters were left in place and further chemotherapy was instituted. The patient, however, developed deep vein thrombosis and hepatic failure due to disseminated malignancy and expired 4 weeks later.

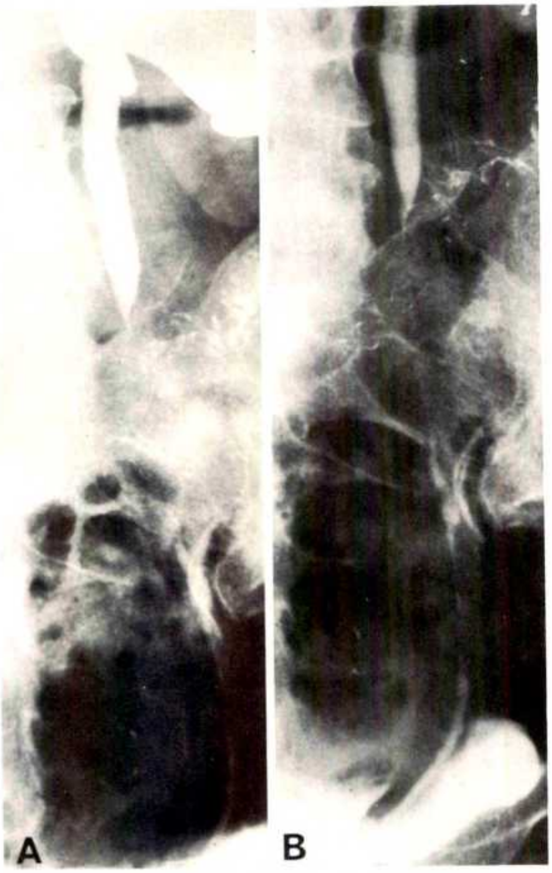

Fig. Left retrograde ureterogram reveals obstruction at the level of the sacroiliac joint (A) with a proximally dilated ureter and hydronephrosis (B).

Comment

In a series of 6000 patients with all stages of breast cancer only 24 had clinically recognisable ureteric obstruction secondary to metastatic disease (Grabstald and Kaufman, 1969). Retroperitoneal fibrosis due to metastatic malignancy can also occur with carcinoma of the colon, lung, stomach, pancreas and prostate (Thomas and Chisholm, 1973). The ureteric obstruction is usually due to a sclerotic reaction to the malignancy in the periureteric fibroadipose tissue and not due to direct invasion of the lumen. Management in such cases has to be on an individual basis and is usually governed by the overall prognosis and the extent of the primary tumour. However, retroperitoneal fibrosis secondary to metastatic disease should be differentiated from idiopathic retroperitoneal fibrosis, since in the latter condition ureterolysis with or without subsequent steroid therapy provides excellent results (Srinivas and Dow, 1983).

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Requests for reprints to: Dr V. Srinivas, Department of Urology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021, USA.

Malignant Penile Haemangio-endothelioma

A. G. MAICHE, P. GRÖHN and J. MÄKINEN, *Department of Radiotherapy and Oncology, University Central Hospital, Helsinki, Finland*

Case Report

In April 1975 a 30-year-old man noticed a small lump in the shaft of his penis. Two years later the lump grew rapidly to 6 cm in diameter. The patient was admitted to hospital with a diagnosis of haematoma. The only symptom was pain during erection and after coitus. The tumour occupied the whole of the shaft of the penis. Histological examination revealed a tumour of mesenchymal origin, rich in blood vessels and with considerable mitotic activity. The diagnosis of angiosarcoma was established. Clinical investigation showed no sign of metastases.

Amputation of the penis was performed. Histological examination showed a malignant haemangio-endothelioma with spread to the corpus cavernosum.

A local recurrence in the scar was noted 11 months later and treated by radiotherapy with ^{60}Co up to 66 Gy in 33 fractions. Lung and bone metastases were noted during radiotherapy. Chemotherapy with VAC (vincristine, Adriamycin, cyclophosphamide) was given with a partial response lasting 8 months. The patient later received DTIC, high dose methotrexate, actinomycin-D and cisplatin without apparent effect. He died 28 months later.

Comment

The incidence of penile cancer in Finland is very low (0.8/100,000). Angiosarcomas comprise about 3% of all soft tissue sarcomas. The prognosis is poor, with the mean disease-free survival less than 2 years and the 5-year survival rate about 25% (Aust, 1979). In Finland there are no previously reported cases of penile angiosarcoma and only a few cases have been reported (Deutsch *et al.*, 1973). According to modern concepts, combination therapy with surgery, possibly radiotherapy and adjuvant chemotherapy is recommended, especially for anaplastic soft tissue sarcomas and for patients with penile sarcomas.

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Requests for reprints to: A. G. Maiche, Department of Oncology and Radiotherapy, University Central Hospital, Haartmaninkatu 4, SF 00290 Helsinki 29, Finland.

The Management of Massive Haemorrhage Following Transurethral Resection of Prostate in the Elderly

W. MALONE and M. DUNN, *Department of Urology, Queen's Medical Centre, Nottingham*

Case Report

A 74-year-old-man presented with a 2-year history of severe prostatism. The prostate felt malignant and a biopsy was taken. He was admitted overnight because of rectal bleeding but this rapidly settled. Blood coagulation studies were normal. He was admitted for prostatectomy 3 months later. The procedure was difficult owing to excessive bleeding but transurethral resection was completed. He continued to bleed, so a laparotomy was performed and the prostatic cavity was packed. Six hours later bleeding became so severe that both internal iliac arteries were ligated and the prostatic capsule was compressed by packs placed inside and outside the capsule.

The urine was sterile both pre-operatively and per-operatively. The thrombin time was raised and the blood platelet count was reduced to 30×10^9 mmol/l but there was no hypofibrinogenaemia. A blood sample took over 4 h to clot *in vitro*.

The patient continued to bleed and by the fourth post-operative day 54 units of blood had been transfused. Exploration of the drain site revealed a small superficial spurting artery which was ligated. The packs were removed after 5 days but bleeding recommenced and further transfusions were given for 72 h, when quite suddenly the bleeding stopped. By then 85 units of whole blood and 22 units of platelets and fresh frozen plasma had been transfused.

When the catheter was removed he passed urine satisfactorily and he was discharged home fit and well. Repeat coagulation and clotting studies were normal.

Comment

The patient later revealed that minor cuts bled for 2 or 3 days before healing but no other members of the family had known bleeding or coagulation disorders. Post-operatively his blood took over 4 h to clot and disseminated intravascular coagulation was considered, but haematological investigations showed only increased thrombin time and thrombocytopenia without hypofibrinogenaemia. Histology of the prostatic chippings showed benign prostatic hypertrophy.

Pickens and Lattimer (1972) implicated disseminated intravascular coagulation as a cause of post-prostatectomy bleeding and recommended treatment with heparin, whereas epsilon aminocaproic acid was recommended by O'Sullivan and Joyce (1972) with blood transfusion, plasma factor replacement, heparin and ligation of the internal iliac arteries if necessary. Epsilon aminocaproic acid has been shown to reduce post-operative blood loss but tranexamic acid, the more potent antifibrinolytic agent, is not recommended (Ward and Richards, 1979).

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Requests for reprints to: M. Dunn, Department of Urology, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH.

British Journal of Urology (1986), **58**, 234-235
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Notices

British Association of Urological Surgeons and Canadian Urological Association

Presidents: Professor J. P. Blandy, MA, DM, MCh, FRCS, FACS
Dr G. A. Farrow, MD, FRCS(C), FACS

Annual Meeting: London, 17–20 June 1986

All correspondence to: R. G. Notley, MS, FRCS, Honorary Secretary, British Association of Urological Surgeons at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Shackman Travelling Fellowships 1987

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited Training Programme in Urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent University status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to Urology or to Renal Transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1986.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

Fifth Basic Urodynamics Course

Bristol. 12 April 1986

The topics will include:

Anatomy and physiology
Basic techniques
Urodynamic equipment
Clinical applications in urology, gynaecology and spinal injuries

Further particulars from: P. Abrams, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

Athenian Days of Urology 1986

Athens, Greece. 9-11 May 1986

The topics will be:

(1) What's new in urology?
(2) Extracorporeal lithotripsy.

Further information from: Professor C. Dimopoulos, Laikon Hospital, 11527 Athens, Greece.

Multidisciplinary Course on the Principles of Cancer Treatment

London. 2-5 June 1986

Further details from: Courses Department, British Postgraduate Medical Federation, 33 Millman Street, London WC1N 3EJ.

International Symposium on Paediatric Urology

Barcelona, Spain. 18-20 June 1986

Further information from: Dr Gosalbez, Fundación Puigvert, Cartagena 340, 08025 Barcelona, Spain.

Fourth International Forum of Andrology

Paris, France. 19-20 June 1986

The following topics will be discussed:

Prostatitis, acute and chronic
Male contraception
Male sterility: hormonal causes
What's new in andrology (posters)

Further particulars from: Professor G. Arvis, Department of Andrology-Urology, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, F-75012 Paris, France.

Workshop on Testicular Tumours

Copenhagen, Denmark. 16–19 August 1986

The programme will include lectures and free communications on the following topics: morphology and function of the germ cell, cell lines, chromosome markers and oncogenes, histochemistry and monoclonal antibodies, carcinoma *in situ*, screening, prognostic factors, treatment, toxicity, and fertility.

Further information from: Dr M. Rørth, Department of Oncology II, Finsen Institute, 49 Strandboulevarden, DK-2100 Copenhagen, Denmark.

Sixth International Congress of Cryosurgery

Athens, Greece. 4-6 September 1986

Further information from: Professor C. Dimopoulos, Sismanoglion Hospital, Maroussi, Athens, Greece.

First Symposium on Morphological Basis of Human Reproductive Function

Fiugge Terme, Italy. 11-12 September 1986

Further information from: Professor G. Spera, V Clinica Medica, Policlinico Umberto 1, Università "La Sapienza", 00161 Rome, Italy.

International Society for Dynamics of the Upper Urinary Tract

Newport, USA. 14-16 September 1986

Further information from: Dr B. L. R. A. Coolsaet, Noordheuvel 50, 2170 Wuustwezel, Belgium.

42nd Congress of Swiss Association of Urology

Luzern, Switzerland. 18-20 September 1986

The following topics will be discussed:

Hypospadias
Disturbances of bladder function (together with Swiss Society of Pediatric Surgery)
The septic patients (together with Swiss Society of Surgery)
Free communications

Further particulars from: Professor K. Bandhauer, Klinik für Urologie, Kantonsspital, CH-9007 St. Gallen, Switzerland.

British Journal of Urology (1986), **58**, 236-238

Book Reviews

Tropical Urology and Renal Disease. Edited by I. Husain. Pp. xiv + 435. Edinburgh: Churchill Livingstone. 1984. Price £30.00.

This is a first class book which most urologists will want in their own library; it will be especially welcomed by those who visit, examine or practise in that extensive part of the world covered by the "tropics". Many of the contributors are based in the Middle East but others are from Bombay, Yaounde, Kampala, Bangalore, Kuala Lumpur, Hong Kong, San Juan and even Leeds.

The contents are arranged in seven sections: section 1 opens with a useful discussion on the patterns of pathology in the tropics and the investigation of these particular problems. The high proportion of stones, lower genitourinary infections and bilharziasis immediately dictates the main sections of this book and these subjects are dealt with comprehensively. A section on other parasites in the genitourinary tract provides an excellent reference source for those who may not be familiar with these problems. Other common problems that have a high prevalence in the tropics, such as genital lesions, carcinoma of the penis, urethral strictures and urinary-vaginal fistulae, are authoritative. Whether or not a section on renal failure is appropriate is arguable, but the contributions are interesting and give some important information relevant to either a tropical or third world practice. Prostatitis is dealth with in a concise summary but does not convey the extent of the problem presented by some patients who have travelled far and wide and received prostatic massage, rectal faradism, etc, etc, and still have symptoms. A further small deficiency is that there is virtually no comment on infertility which, although not restricted to the tropics, can create serious social problems in some countries. There are six useful appendices covering instruments, sterilisation, sanitation, drugs and records.

It is estimated that between two to three hundred million people in 71 countries are infected with bilharzia. The sheer magnitude of this and many other tropical urological problems makes a book such as this all the more important. It is highly recommended for individuals and libraries.

Clinics in Obstetrics and Gynaecology. Volume 12, No. 2: Gynaecological Urology. Edited by S. Raz. Pp. ix + 529. Eastbourne: Saunders. 1985. Price £16.25.

It must be unusual to find the contents of two different books to be identical. However, the publishers of the Clinics series felt that because the contents were relevant to both gynaecologists and urologists, they should also be published in the May 1985 issue of Urologic Clinics of North America. This seems a good decision, for the contents are of considerable interest to urologists and indeed 15 of the 19 authors are urologists. As in most Clinics books, the aim is to cover the topic comprehensively by experts in the field. This aim is achieved and this (or the Urologic Clinics) book is highly recommended as an up to date reference for these urological problems.

Advances in Non-invasive Nephrology. Edited by G. Lubec and V. Campese. Pp. xi + 300. London, Paris: John Libbey. 1985. Price £30.00; US $53.00; FFr 385.

This interesting title contains the Proceedings of an International Congress on Non-invasive Diagnosis of Kidney Disease, held in Vienna in September 1983. The contents comprise 64 short chapters that cover imaging, from NMR (MRI) to radionuclides, a comprehensive number of biochemical methods, including urinary enzymes and a small section on immunology. The title will probably deter the urologist but there are chapters on renal function in renal colic, the localisation of urinary tract infections, TPA in urological cancers and tests for renovascular hypertension that are of interest to readers of this journal. A substantial proportion of the book is devoted to diagnostic methods relating to patients either on dialysis or after renal transplantation. The range of diagnostic tests that come under this title is remarkable and these short chapters provide a useful reference source for anyone with nephro-urological interests.

Genitourinary Cancer. Contemporary Issues in Clinical Oncology. Volume 5. Edited by M. B. Garnick. Pp. xiii + 280. Edinburgh: Churchill Livingstone. 1985. Price £39.00.

This book is the fifth in a series of Contemporary Issues in Clinical Oncology. The opening sentence of the preface states that the aim is to produce a practical, clear, concise and useful series that will provide the physician with a state of art and science base to design treatment for today's patients . . . (*sic*). Some urologists might be intimidated by such a statement. They should, however, take heart and read on, since this volume reviews the recent and rapid progress in the management of tumours of the testis and draws attention to the changes that seem about to occur in the management of invasive and non-invasive bladder cancer. The review of prostatic cancer is more muted and comment on the progress in cancer of the kidney is, quite correctly, remarkable for its absence in so far as allusion is made to the possible role of interferon therapy.

Ever urologist should familiarise himself with the general outline of this work, if only to be reminded of the fact that progress in the management of urological cancer is occurring largely from innovations in medical treatment rather than from any extension of surgical expertise.

Those particularly interested in urological oncology will find something in every chapter. For the more generally inclined, the chapter on Orchiectomy Alone for Stage I Nonseminomatous Germ Cell Tumours should be read with care and the chapters on Chemotherapy and Prostatic Cancer, Intravesical Chemotherapy and Superficial Bladder Cancer and the Use of Interferon in Urological Malignancies are equally well written and broadly based assessments of the present state of knowledge.

Fluid Electrolyte and Acid-base Disorders. Volumes I and II. Edited by A. I. Arieff and R. A. DeFronzo. Volume I: pp. xxi + 659. Volume II: pp. xxi + 661-1246. Edinburgh: Churchill Livingstone. 1985. Price £125.00.

This book is divided into three sections. The first occupies the whole of Volume I and is entitled "Normal Water and Acid-base Regulation" but includes much material on abnormalities such as oedema, hypo- and hyper-osmolar states, alkalosis and disturbances in potassium, calcium and magnesium metabolism. Section 2 discusses specific pathological states such as renal failure, ketosis, endocrine disorders and the complications of dialysis. Section 3 is called "Special Considerations" and considers the effects upon water and electrolyte metabolism of age, drugs and parenteral nutrition.

The book is intended for nephrologists but it can provide urologists with a sound working knowledge of disorders of the body fluids and will serve them well as a reference volume.

Atlas of Urinary Sediments. Diagnosis and Clinical Correlations in Nephrology. By G. Piccoli, D. Varese and M. Rotunno. Pp. xii + 210. New York: Raven Press. 1984. Price US $77.00.

The aim of this book is to encourage wider use of the examination of urinary deposits as an adjunct to sophisticated biochemical analyses in the diagnosis of renal disease. For residents performing this simple side-room test many unstained photographs have been used to help in the wallpaper matching. Pathologists or cytologists screening urine samples would probably benefit from more Papanicolaou stained preparations and preferably without the rather bright blue backgrounds.

There are three main sections to the Atlas. The first is on morphology of the urinary constituents, the second on crystals and the last part on some diagnostic features in specific nephropathies. The structure of red cells is dealt with in considerable detail and the morphology of casts is abundantly illustrated. The sub-section on crystals is excellent. The brief descriptions opposite the splendid photographs will form a good reference manual for clinicians and laboratory workers alike.

The authors stress how useful examination of the urine can be in acute glomerular disease. Urine reflects the histology of the kidney and its sequential analysis may diminish the number of biopsies required. It is a pity that more photomicrographs of histological sections of the kidney were not included in the discussion of nephropathies alongside their cellular counterparts. Only two were used—both of chronic pyelonephritis. Their presence would have broadened the readership of the Atlas.

Testicular and Epididymal Pathology. By M. Nistal and R. Paniagua. Pp. vii + 358. New York: Thieme-Stratton. 1984. Price DM 198,-.

This is a comprehensive monograph with a good review of normal *in utero* and pre-pubertal testicular development and normal anatomy, biochemistry, histology and ultrastructure. Good advice is given on the proper surgical and pathological handling of testicular biopsies.

Clinicopathological aspects of disease processes are discussed in depth, including defects of steroidogenesis and end organ insensitivity to androgens. Congenital abnormalities, whether confined to testis and genitalia or as part of multisystem clinical syndromes, are fully described. Conditions causing infertility are discussed throughout the book.

In the section on inflammatory diseases, the response to many different agents is described; syphilitic changes are mentioned but not the features of mumps orchitis, which is more relevant at the present time. A review of testicular and paratesticular tumours is included, though not in depth, but it is pleasing to see that prognosis incorporates response to modern therapy. The effects of radiation and drug therapy on the normal testis are also described.

This book would have benefited from an introductory overview of testicular pathology and causes of infertility. Otherwise, it is an excellent treatise, with an emphasis on non-neoplastic conditions, and it should be a valuable textbook for all clinicians and pathologists dealing with childhood and adult testicular disease.

Introduction to Dialysis. Edited by M. G. Cogan and M. R. Garovoy. Pp. xii + 303. Edinburgh: Churchill Livingstone. 1985. Price £38.00.

The aims of this book are "To acquaint those charged with the care of renal failure patients with the principles of sound dialytic therapy" and "to convey how a quantitative understanding of the dialysis process can be translated into good rational clinical care".

There is an adequate description of dialysers, delivery system, access for haemodialysis and peritoneal dialysis, and the management of complications in dialysis. There is also an excellent account of the use of peritoneal dialysis in acute and chronic renal failure, providing practical guidelines for this technique. Unfortunately, the description of haemodialysis in acute and chronic renal failure is mainly an outline of mathematical modelling of haemodialysis, with no practical guidelines for its use. Since sound dialysis therapy can be, and is, practised without the use of computer programs, it is unlikely that this chapter will be of much value as a guide to the use of haemodialysis, particularly to those unfamiliar with the technique. The book ends with a brief outline of the use of dialysis in drug overdosage and a table indicating the clearance by dialysis of commonly used drugs, but without much guidance for the use of drugs in renal failure. The section on drug overdosage seems a little out of place and it might have been more appropriate to have a section on the use of drugs in renal failure.

Unfortunately, while the authors have achieved their objectives, in so doing they have produced a book which lies between a concise textbook and a large reference book. Both because of this, and the rather impractical guidelines for haemodialysis, the reviewer feels this book is unlikely to find a large audience. With the exception of the section on peritoneal dialysis, it is unlikely that urologists will find this a particularly valuable book.

Books Received

Incontinence. By R. C. L. Feneley and J. P. Blannin. Pp. viii + 66. Edinburgh: Churchill Livingstone. 1984. Price £1.75.

Les Polyglobulies. Edited by Y. Najean. Pp. 143. Paris: Masson. 1985. Price 155 Fr francs.

Actualités Chirurgicales. Volume 4. Edited by M. Malafosse. Pp. vii + 211. Paris: Masson, 1985. Price 197 Fr francs.

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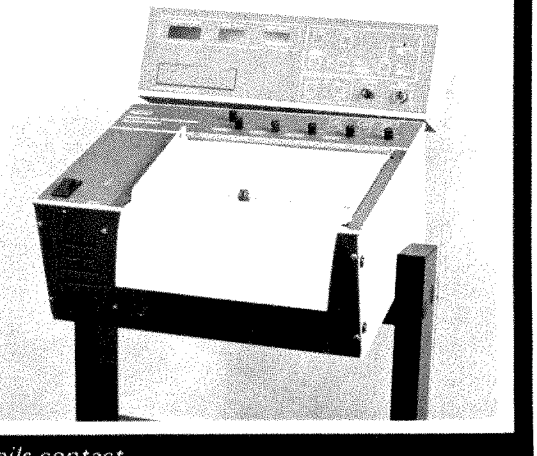

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TECHNICAL DATA

DATA SHEET

PDS* (Polydioxanone) Sterilised Absorbable Synthetic Monofilament Suture

Presentation
PDS (Polydioxanone) Monofilament Synthetic Absorbable Suture is prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding D & C blue No 6 (gauge 0.2 metric and 0.3 metric) D&C violet No 2 (gauge 0.4 metric to 5 metric) during polymerisation. These sutures may also be manufactured undyed (clear).

PDS (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass.

Data obtained from implantation studies in rats show that, at two weeks post implantation, approximately 70% of the suture strength is retained whilst at four weeks the strength retention is approximately 50%. At eight weeks approximately 14% of the original strength remains. *This indicates a significantly longer period of wound support than previously available with an absorbable suture.*

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within six months.

Uses
PDS (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal mucosal sutures could cause localised irritation if left in place for longer than 10 days and should be removed as indicated. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

The safety and effectiveness of PDS (Polydioxanone) sutures in neural and cardiovascular tissue have not yet been established. The use of this material in the renal tract is currently under investigation.

Pharmaceutical Precautions
Do not resterilise.

Legal Category P
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Packaging
The gauge range available will be 0.3 metric (9/0) to 5 metric (2). Various lengths of material attached to non traumatic stainless steel needles are packaged in sealed aluminium foil sachets.

The primary pack is sealed within a peel-apart secondary pouch and contained in a film-wrapped drawer style carton.

Further Information
So suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos PL 0508/0011 (dyed); PL 0508/0012 (clear).

Br Pat No 1 540 053.

Date of preparation of Data Sheet—September 1982.
Revised 1/1985.

DATA SHEET

Coated VICRYL* (Polyglactin 910) Sterilised Absorbable Synthetic Braided Suture

Presentation

The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

Coated VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Suture may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action
Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses
Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration
By implantation.

Contra-indications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissue under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 10 days and should be removed as indicated.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) Sutures in neural tissue and in cardio-vascular tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category P
Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities
Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sales is 12 packs contained in a film wrapped drawer style carton.

Further Information
No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

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Date of preparation of Data Sheet - April 1981
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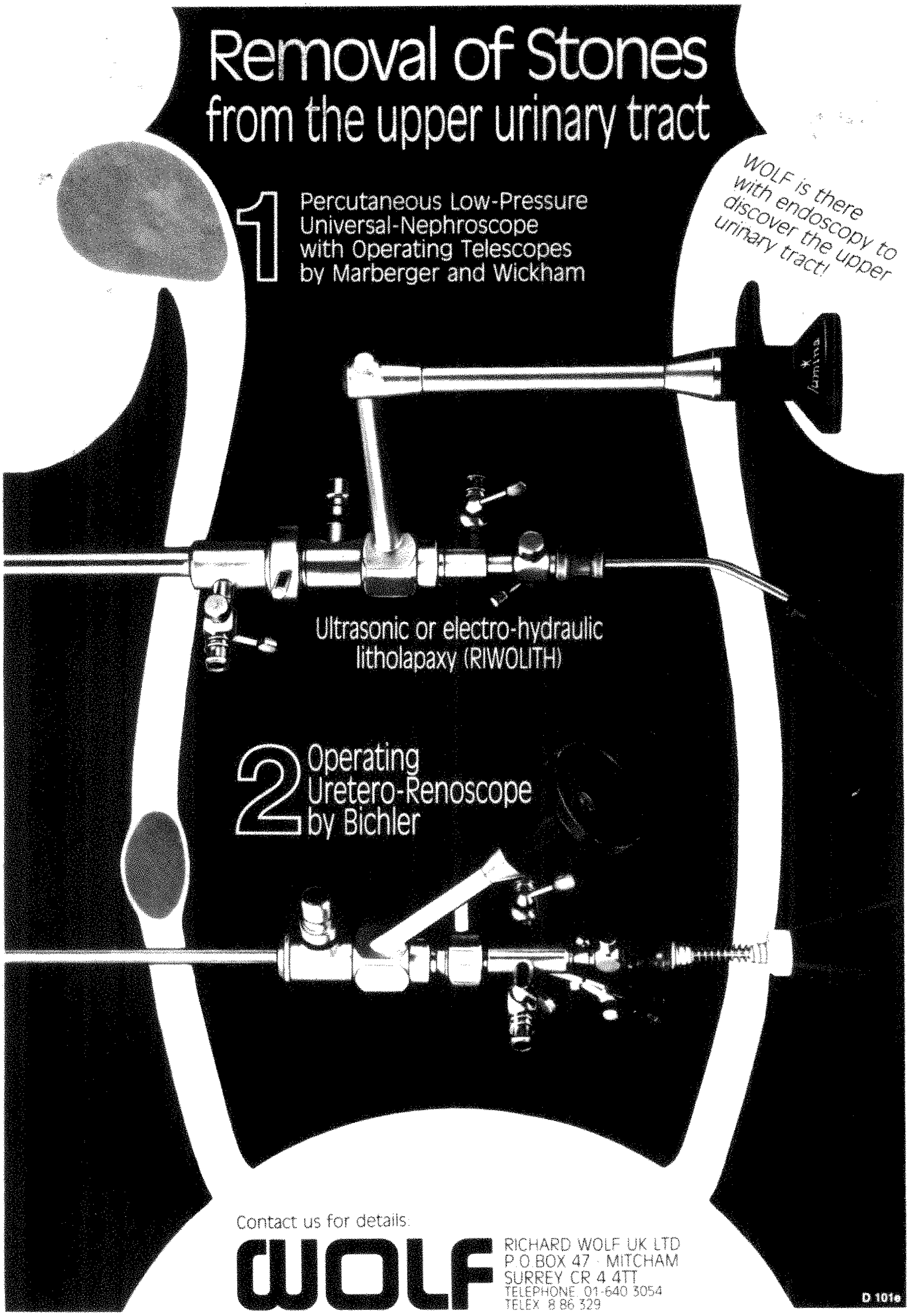

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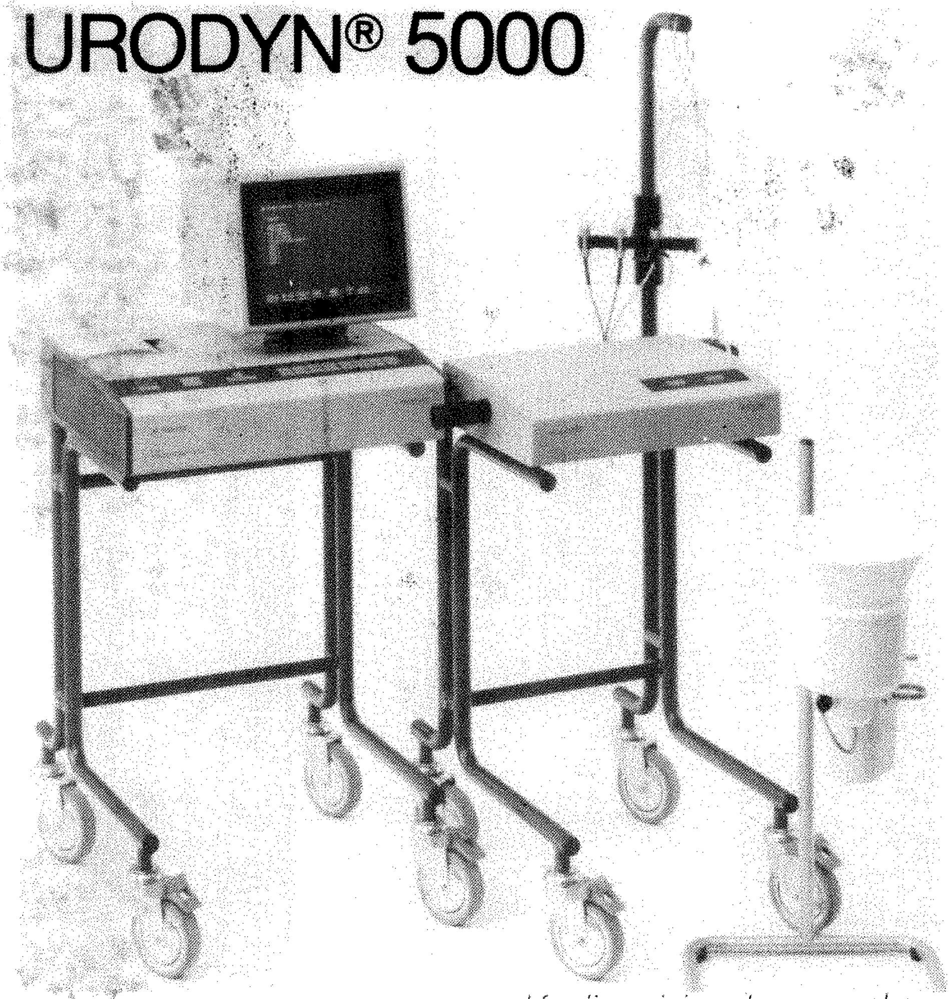

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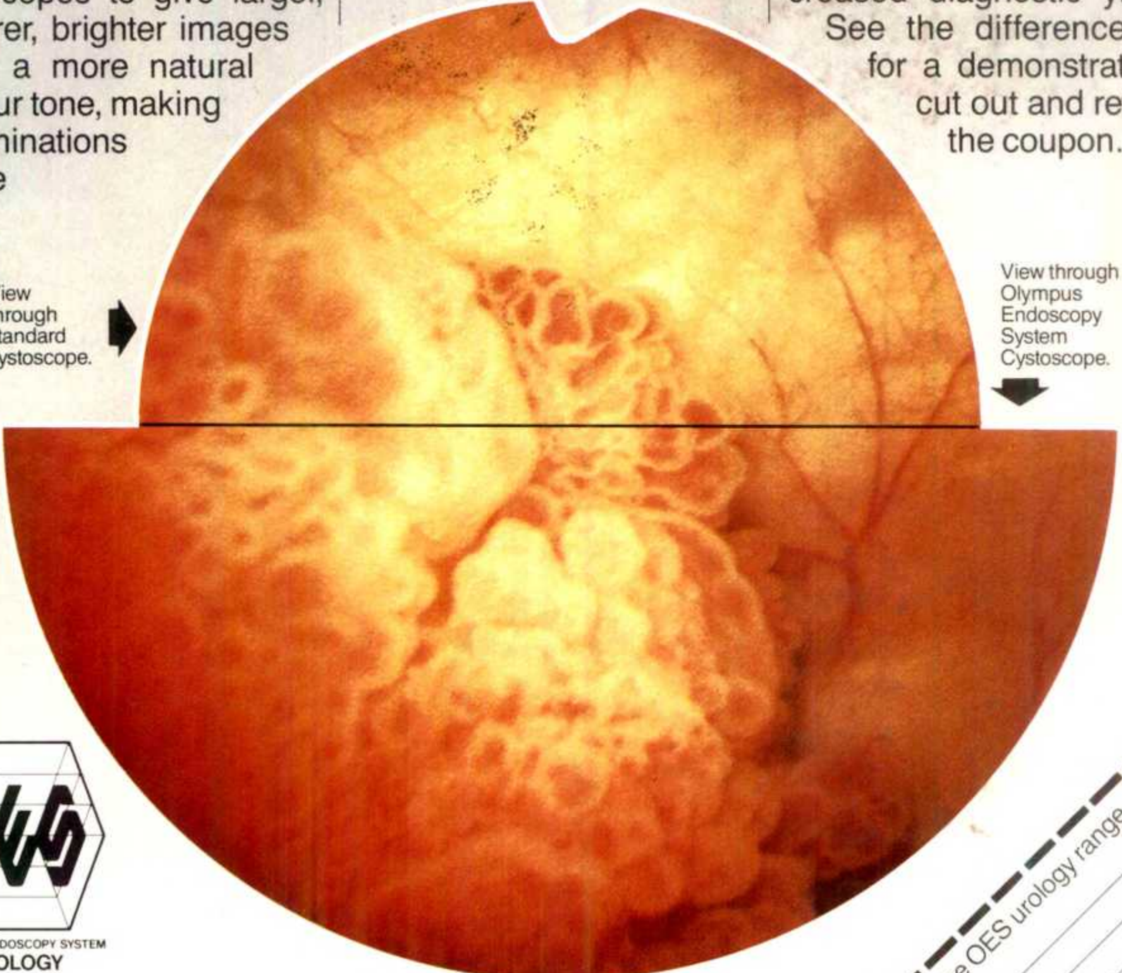
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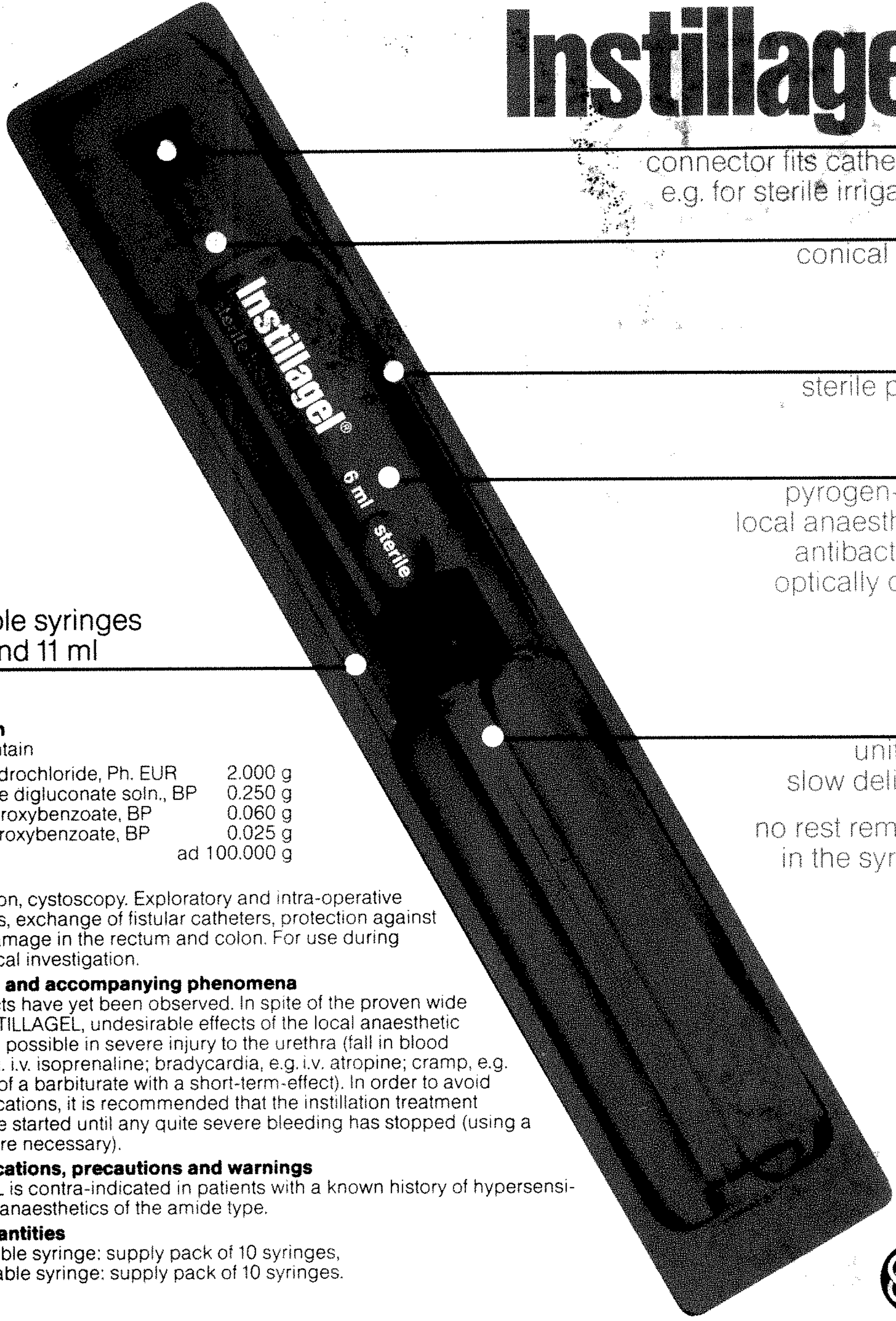

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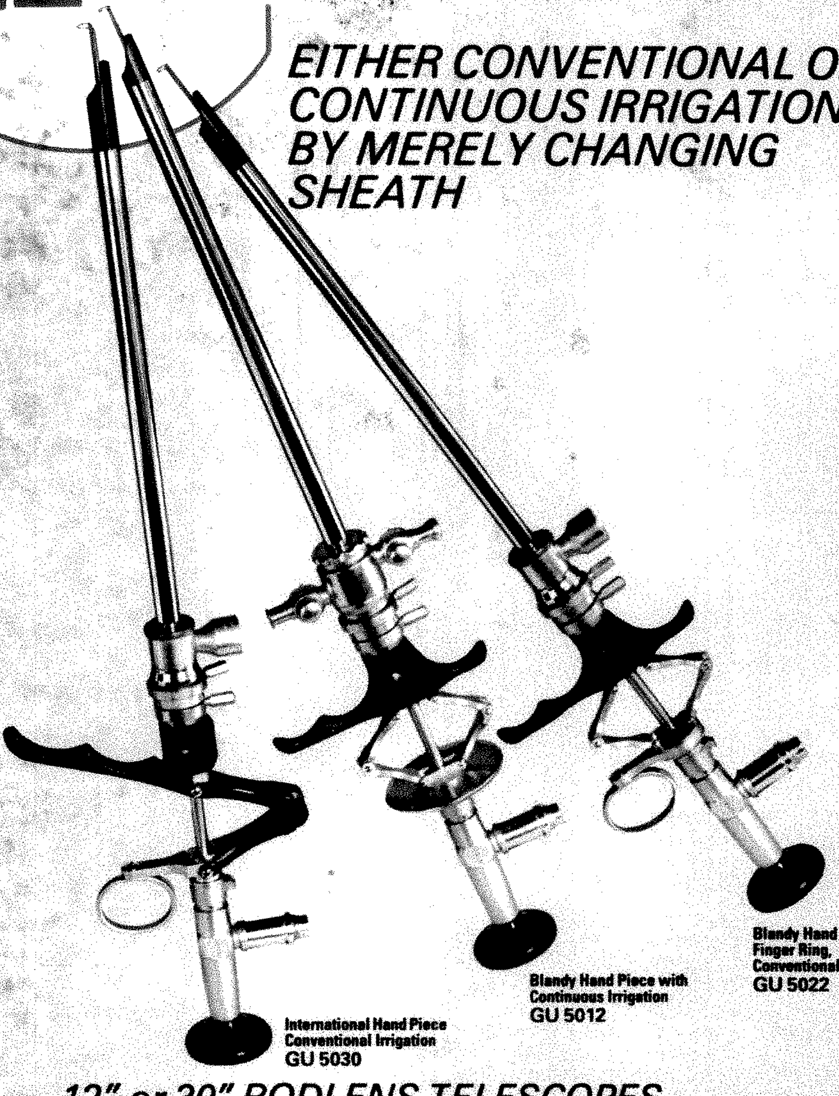

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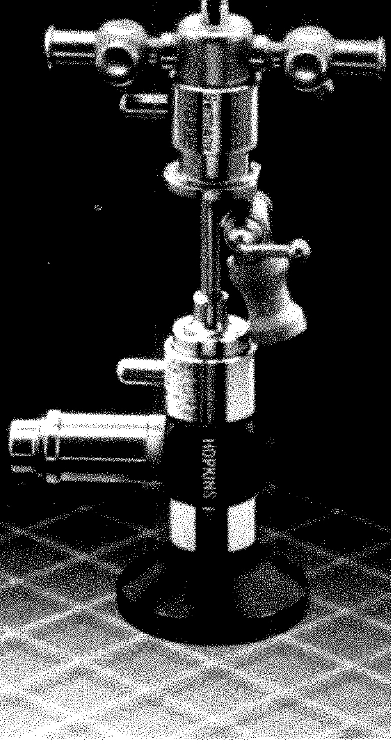

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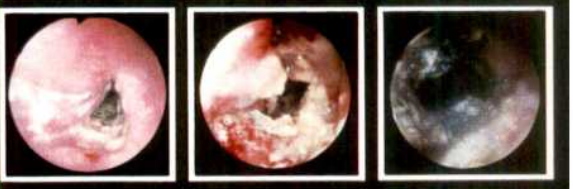

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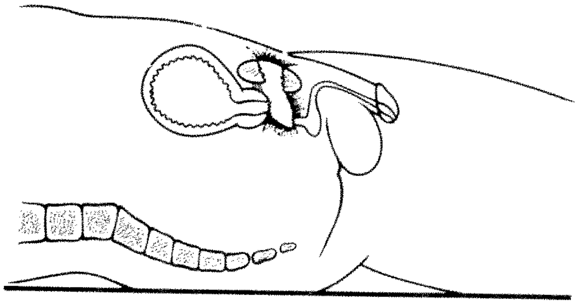

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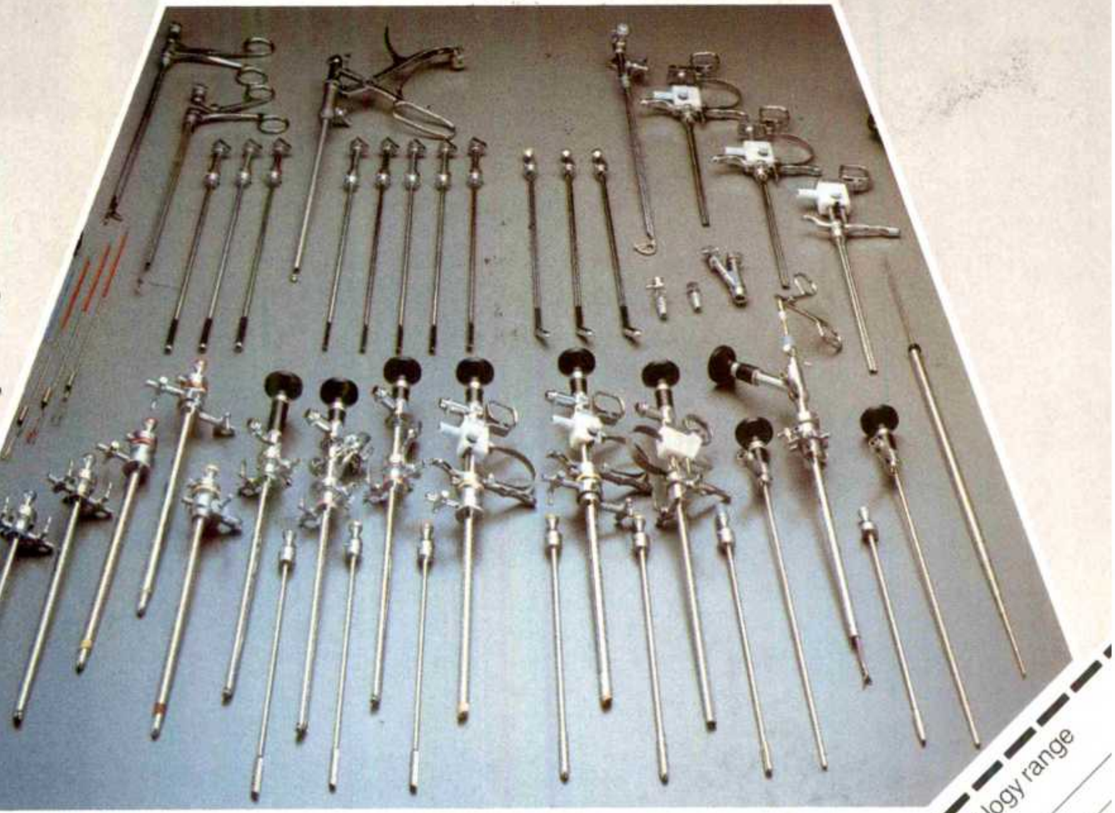

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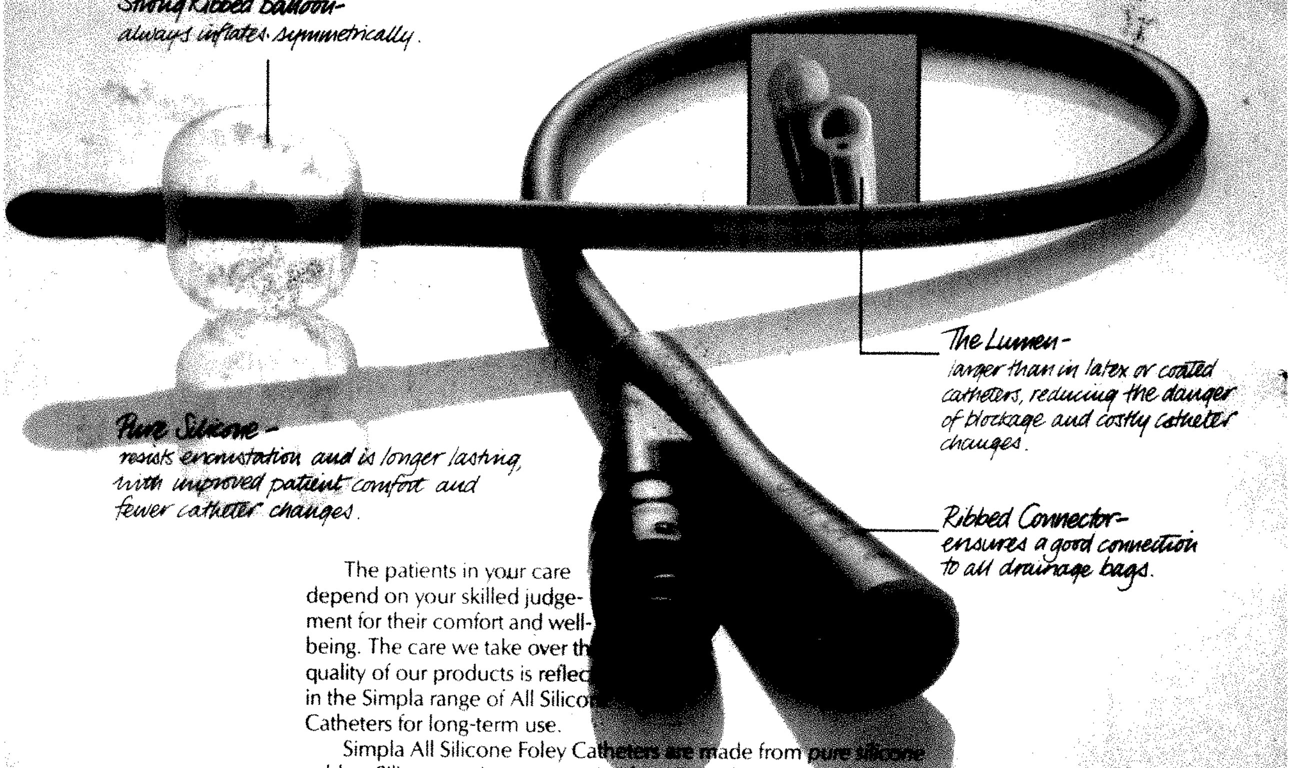
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REVIEW

Interstitial Cystitis

F. PARIVAR and R. A. BRADBROOK

Department of Urology, Torbay Hospital, Torquay

Interstitial cystitis is an uncommon condition and hence its demography is rather vague. It produces some of the most disabling symptoms experienced by urological patients, characterised by severe frequency, dysuria, lower abdominal and urethral pain. It affects both women and men, although only 10% of patients are male. Whilst the peak of the disease is between 30 and 50 years (Oravisto, 1980) it has also been reported in children (Geist and Antolak, 1970).

History

In 1915 Hunner reported on "A rare type of bladder ulcer" in eight women who had symptoms of intense cystitis resistant to all conventional forms of treatment. His patients had two types of ulcers. The first was a solitary ulcer or group of ulcers with a granulomatous base and hyperaemic periphery, while the second type was a white scar surrounded by a hyperaemic area. At cystoscopy the ulcers appeared to be superficial but at operation they were found to be deep, involving the whole thickness of the bladder wall. These ulcers are still the hallmark of diagnosis of interstitial cystitis and are still known as "Hunner's ulcers".

Aetiology

The aetiology of interstitial cystitis is obscure. The absence of any detectable bacterial urinary infection is a prerequisite for its diagnosis. No evidence has ever been found of a viral or fungal agent.

Inheritance does not seem to play a role in the development of interstitial cystitis. There has been only one reported case of the disease developing in monozygotic twins and another developing in a mother and daughter (Oravisto, 1980). A neurogenic cause for interstitial cystitis has been postulated in the past and this led to operations such as sacral neurectomy and posterior rhizotomy. In the light of present knowledge a neurogenic cause appears unlikely.

In recent years growing evidence has emerged of a possible autoimmune origin for interstitial cystitis. This has been supported by the discovery, in some patients, of antibodies against bladder mucosa, which are not found in patients with bacterial cystitis (Silk, 1970). Mattila *et al.* (1983) found the classical vascular endothelial changes seen in autoimmune disease to be present in 70% of their 20 patients with interstitial cystitis.

There are two categories of autoimmune disease: organ-specific (*e.g.* thyroiditis) or non-organ-specific (*e.g.* systemic lupus erythematosus). However, interstitial cystitis falls between the two groups by being organ-specific with no organ-specific antibodies (Oravisto, 1980). There are several features of interstitial cystitis common to other autoimmune diseases: 90% of patients are female, which is typical of autoimmune disease. There is a high incidence of systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, scleroderma and autoimmune thyroiditis in patients with interstitial cystitis. Allergies, especially to drugs, have been reported in 26 to 70% of cases (Rosin *et al.*, 1979; Oravisto, 1980), and 53 to 85% have evidence of antinuclear antibodies (Oravisto, 1980). Histological changes in the bladder wall are consistent with connective tissue disease (*i.e.* infiltration by lymphocytes, plasma cells, mast cells and eosinophilis in varying degrees). Finally, most therapeutic measures employed in the treatment of autoimmune diseases have at some stage in the past been used in the treatment of interstitial cystitis with varying degrees of success. These include ster-

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oids, non-steroidal anti-inflammatory agents and azathioprine.

Pathology

The original "elusive ulcer" that Hunner described was on the anterior wall or vault of the bladder. It is now evident that the ulceration may occur in any part of the bladder, but it is not a prerequisite for the diagnosis. It is also recognised that there is a spectrum of this disease as described in 1978 by Messing and Stamey, who also produced a classification of the disease. Most patients present at a stage when the bladder (measured capacity under anaesthesia) is normal and there are no ulcers. These patients have pinpoint areas of petechial haemorrhage throughout the bladder mucosa which appear only on distension at cystoscopy. The remainder present with late disease, with a reduced bladder capacity and the classical ulceration. There is no definite evidence that the former group will eventually progress to the latter.

The histological appearances of interstitial cystitis are non-specific. Probably the most consistent feature is submucosal oedema and vasodilatation (Messing and Stamey, 1978). There is a varying degree of fibrosis in the mucosa and muscle layer with infiltration by round cells as well as plasma cells and eosinophils. The mast cell count is increased (Larsen *et al.*, 1982) and in severe cases large areas of epithelium are lost (Oravisto, 1980). It has been suggested that histological estimation of mast cells in the detrusor muscle is of value in establishing the diagnosis (Larsen *et al.*, 1982). More than 20 mast cells per square millimetre of muscle tissue gives a diagnostic specificity of 88% and diagnostic sensitivity of 95% (Kastrup *et al.*, 1983).

Electron microscopy shows pronounced vascular endothelial injury with basement membrane proliferation and neogenesis of elastic tissue (Mattila *et al.*, 1983).

Diagnosis

Diagnosis is based on the symptom pattern, cystoscopic findings and histology. Symptoms, which are commonly severe and disabling, include frequency, urgency, nocturia, dysuria, haematuria and suprapubic or perineal pain (Messing and Stamey, 1978), partially relieved by voiding. It has been noted that the symptoms are very variable from day to day. The onset of the disease is often acute, mimicking acute urinary infection, and patients have often received several courses of antibiotics before they are referred.

Physical examination is generally normal. Some authors have described anterior vaginal and urethral tenderness on pelvic examination (Lapides, 1975) as important findings. Radiological contrast studies, bacteriology and urodynamic studies play only a small part in making a positive diagnosis of interstitial cystitis. They are, however, useful in excluding other urinary pathology.

Cystoscopy is the most important diagnostic measure in this disease. Bladder capacity under anaesthesia may be normal or as low as 50 ml. Hunner's ulcers are present in some cases but in many patients the bladder may look normal on first inspection with minimal mucosal injection only. After two or three distensions, however, the pinpoint petechial haemorrhages or glomerulations become visible. These coalesce and bleed when the bladder is distended. It is very important to assess the severity of the disease endoscopically, since it is the patient with a small contracted bladder who is least likely to respond to treatment.

Although histology is fairly non-specific, a bladder biopsy is important to exclude other conditions which can resemble interstitial cystitis, especially carcinoma *in situ*, tuberculosis, schistosomiasis and malakoplakia. There is no evidence that interstitial cystitis may give rise to carcinoma (Murphy *et al.*, 1982).

Treatment

Hunner (1915), having noticed the lack of response to conventional treatment, recommended local excision of the ulcers. However, this can involve multiple and often extensive resections of the bladder, with no guarantee of cure. Hunner later recommended topical application of silver nitrate to the ulcer and even electrical cauterisation.

Because the aetiology of interstitial cystitis is uncertain, the treatment of the disease is both difficult and unsatisfactory. Nowadays the uncertainty as to the aetiology has led to a myriad of different treatments (Table).

(1) *Oral drugs*

Proponents of an autoimmune aetiology have used steroids and azathioprine. In one series, 19 of 25 patients reported a sustained improvement on long-term prednisolone (Badenoch, 1971). However, other observers have failed to achieve the same success rate. Response to azathioprine has

Table Available Treatments for Interstitial Cystitis

Conservative		
1. Drugs		
	(a) Oral	Steroids
		Azathioprine
		Antihistamines
		Anticholinergics/antispasmodics
		Anti-inflammatory
		Tranquillisers
		Narcotics
		Sulphopentosan sodium (Elmiron)
	(b) Intravesical	Oxychlorosene
		DMSO
2. Electrical stimulation		
Surgical		
1. Endoscopic		Fulguration or resection of ulcers
		Injection with saline, heparin or steroids
		Bladder distension
2. Open surgery		Partial cystectomy
		Intestinal cystoplasty
		Cystolysis
		Cysto-cystoplasty
		Urinary diversion—with cystectomy
		—without cystectomy
		Neurosurgical techniques—rhizotomy
		—cordotomy
		—sacral neurectomy

been reported as high as 50% (Oravisto and Alfthan, 1976). In view of the excess of mast cells in this condition, antihistamines have been tried and good results claimed (Simmons and Bunce, 1958). Anticholinergics, antispasmodics, non-steroidal anti-inflammatory agents, tranquillisers and narcotics have all been used as adjuvant treatment, with varying degrees of success.

More recently, oral sulphopentosan sodium (Elmiron) has been described as effective treatment for interstitial cystitis. This compound is a synthetic analogue of a sulfonated glycosaminoglycan, which is the natural compound found in the surface mucin of the bladder mucosa. In interstitial cystitis this protective mucin layer is lost. Oral or intravesical administration of this preparation has been shown to replace the protective surface mucin. This drug has been used for more than 2 decades in the treatment of hyperlipidaemia and has anticoagulant properties. Its effect in the treatment of interstitial cystitis was first described by Parsons *et al.* (1983). They showed that 20 of their 24 patients had an 80% reduction in their symptoms within 4 to 8 weeks of starting treatment. Two patients had a 50 to 80% reduction in their symptoms. This preparation is currently undergoing clinical trial.

(2) *Intravesical drugs*

Intravesical instillation of various agents has been tried. The best known agents include oxychlorosene sodium (Chlorpactin WCS-90) and dimethyl sulfoxide (DMSO).

Chlorpactin was first used by Wishard *et al.* (1957) with good results. In a more recent series, 14 of 17 patients treated in this way were either symptom-free or significantly improved. Ten of these 14 patients had associated cystoscopic evidence of healing of bladder lesions (Murnaghan *et al.*, 1969). A 6-year follow-up of these patients has shown that treatment continues to be effective, although further courses were needed. In another series, 72% of patients were symptom-free for at least 6 months following this treatment, most for more than a year (Messing and Stamey, 1978). One-third of these successes required only one instillation of Chlorpactin. All of those patients who responded to the first instillation also responded to subsequent treatments. Instillation of Chlorpactin requires general anaesthesia. One litre of 0.4% oxychlorosene is freshly prepared in the operating theatre just before use. The patient is catheterised and the solution is instilled by infusion under a hydrostatic pressure of 10 cm, until the bladder is full. The bladder is then emptied and instillations are repeated until one litre of the solution has been used (Messing and Stamey, 1978). The second and third instillations should be performed at 4-week intervals to allow the urothelium to regenerate. Subsequent instillations are carried out at weekly intervals and are discontinued as soon as the patient is symptom-free.

Dimethyl sulfoxide (*DMSO*) has also been shown to be useful in the treatment of interstitial cystitis. DMSO was first prepared in 1867 as a by-product of the paper pulp industry, and its main use is as an industrial solvent. It is also known to have anti-inflammatory properties and is used in various topical medications. It was first used in the treatment of interstitial cystitis by Stewart *et al.* (1972) This method of treatment has the advantage that general anaesthesia is not required. The patient is catheterised and 50 ml of a 50% solution of DMSO are instilled into the bladder. The solution is retained for 15 to 30 min, following which the bladder is emptied by voiding. Treatment is given at 2-weekly intervals until symptomatic relief is obtained, at which time the intervals between treatment are increased appropriately. This therapy is simple, effective and inexpensive. Stewart and

Shirley (1976) showed that 74% of their 45 patients had a good to excellent symptomatic response to DMSO, whilst 13% had a poor response. In other series, 12 of 17 patients had dramatic symptomatic relief (Ek *et al.*, 1978) and 19 of 20 patients showed complete symptomatic remission (Fowler, 1981).

(3) *Electrical stimulation*

One other non-invasive method that has been used for controlling the symptoms of interstitial cystitis is electrical stimulation of the bladder. This can be achieved either by placing electrodes on the lower abdomen or transvaginally. A battery operated generator provides continuous pulse stimulation of the region. Fall *et al.* (1980) reported favourable results in their 14 patients, although it involved long-term treatment, in some cases up to 1.5 years.

(4) *Surgical methods*

Surgical methods of treatment of interstitial cystitis involve either endoscopic or open surgery.

Endoscopic surgery Endoscopically the ulcers may be fulgurated or resected: 61% of patients who underwent transurethral resection of the ulcers were free of symptoms for at least 1 year and 15% had no recurrence (Greenberg *et al.*, 1974). Although this technique is not recommended as the sole treatment of the condition, it may be helpful in some cases.

Local injection of hydrocortisone, saline or heparin in and around the ulcer is reported as being helpful. Johnston (1956) produced marked improvement in his patients by injecting the ulcers with hydrocortisone. Weaver *et al.* (1963) reported good results with local injection of saline and heparin. The duration of remission with hydrocortisone is not known, but it can be repeated as many times as required.

Most patients with interstitial cystitis have, at some stage during treatment, had a hydrostatic bladder distension. The mechanism by which this relieves symptoms is not well understood. It is said that prolonged distension produces detrusor ischaemia which results in degeneration of nerve axons within the bladder wall (Sehn, 1976). The clinical response to hydrostatic distension is often dramatic but not long-lived, probably as a result of axonal regeneration. Simple hydrostatic distension of the bladder during cystoscopy may be enough to produce dramatic but transient improvement in symptoms. Dunn *et al.* (1977) showed that 16 of their 26 patients were symptom-free, six were improved and three unchanged by hydrostatic distension. The remission in these patients lasted 3 to 18 months.

Open surgery Open surgery should be reserved as a last resort in patients who have not responded to other forms of treatment. The various methods include partial cystectomy, intestinal cystoplasty, cystolysis, cysto-cystoplasty and urinary diversion with or without cystectomy.

Partial cystectomy alone is of limited value. It involves resection of the diseased part of the bladder, but there is no guarantee that the disease will not recur in the bladder remnant. It also results in a small bladder with its associated symptoms. The end stage of interstitial cystitis is often a contracted bladder, but this can be overcome by augmentation cystoplasty (Gil-Vernet, 1965). Wallack *et al.* (1975) reported two patients who had contracted bladders resistant to other therapy treated successfully by caeco-cystoplasty. Auvert *et al.* (1983), Le Portz *et al.* (1983) and Alno *et al.* (1983) have reported similar success with this technique. However, with an intestinal cystoplasty there is a risk of recurrence of the disease in the intestinal segment of the bladder. This treatment, therefore, is probably best reserved for the patient whose disease has burnt out and who suffers from the "small bladder syndrome". If the bladder is not contracted, Worth and Turner-Warwick (1973) have suggested cystolysis as the treatment of choice. In this procedure the bladder is freed from its surrounding tissues down to the trigone posteriorly by dividing superior and ascending branches of inferior vesical vessels. This presumably divides most of the sensory pathways to the upper part of the bladder. All of their 11 patients had complete relief of pain. Their frequency and nocturia was improved but in only half of the patients was the bladder volume under anaesthesia increased. Freiha and Stamey (1980) have reported similar good results with this technique. Cysto-cystoplasty (supra-trigonal bladder transection, described by Turner-Warwick and Handley Ashken (1967)), has a similar effect.

Urinary diversion should be undertaken only when all other medical and surgical forms of treatment have been tried and have failed.

Neurosurgical techniques to denervate the bladder have enjoyed some popularity. These include pre-sacral neurectomy, post-sacral rhizotomy and anterolateral chordotomy.

Interstitial Cystitis—An Enigma

Although interstitial cystitis has been recognised for many years, the aetiology remains obscure and the pathology non-specific. There is enough evidence to suggest that the condition has an autoimmune basis. Whether this is primary or secondary remains uncertain.

The key feature of interstitial cystitis is the loss of the protective mucin layer of the transitional cell epithelium, the chemistry and physiology of which are currently under investigation.

It is now suggested that the mucin layer overlying the transitional cell epithelium provides the basis of the bladder's protective mechanism against the ingress of bacteria and other foreign materials. It is suggested, as a working hypothesis in interstitial cystitis, that either the mucin layer is destroyed or the transitional cell epithelium loses the ability to produce it. This loss of the mucin layer renders the epithelium more vulnerable to injury from sepsis or trauma and it may be that the autoimmune process has its origin in this mucosal injury.

It is further suggested that the breakdown of the mucin layer may occur under the influence of certain specific micro-organisms, possibly *Chlamydia*. This could account for the usual acute onset of symptoms of interstitial cystitis. In post-menopausal women, who constitute the majority of cases, the mucin layer failure may be related to changes in hormone balance which produce direct changes in the mucin layer or perhaps more likely due to changes in the bacterial flora of the vagina with the ingress of pathogenic enterobacteria. The main impetus for future research should therefore be directed towards a greater understanding of the protective mucin layer of the bladder, the mechanism of its production and the pathological processes by which it may be destroyed.

Further research might usefully be directed towards the bacteriology of the vagina and lower urinary tract in post-menopausal females, together with an investigation into the effects that such bacteria have on the protective mucin layer of the bladder.

The key to the future management of interstitial cystitis seems to lie in the reinstatement of the protective mucin layer. Various agents show promise in this direction. Sodium cromoglycate (Intal, ICI) has been shown to be of some value (Edwards *et al.*, 1986) and the results of current clinical trials with Elmiron are awaited with great interest.

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The Authors

F. Parivar, FRCSE, Surgical Registrar.
R. A. Bradbrook, FRCS, Consultant Urologist.

Requests for reprints to: F. Parivar, Department of Urology, Torbay Hospital, Lawes Bridge, Torquay TQ2 7AA.

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Percutaneous Renal Surgery and Local Radiotherapy in the Management of Renal Pelvic Transitional Cell Carcinoma

C. R. J. WOODHOUSE, M. J. KELLETT and H. J. G. BLOOM

Departments of Urology and Radiotherapy, Royal Marsden Hospital, and Academic Unit, Institute of Urology and St Peter's Hospitals, London

Summary—Six patients with a history of bladder carcinoma and a radiographic filling defect of the pelvicaliceal system have been investigated or treated percutaneously. In two cases of doubtful diagnosis, percutaneous pyeloscopy showed that no pelvicaliceal tumour was present. In four patients with multifocal or recurrent transitional cell carcinoma and difficult clinical problems, intrarenal tumours were cauterised or resected percutaneously. Radioactive iridium wire (^{192}Ir) was inserted into the surgical track to deliver prophylactic irradiation (4500 cGy) to prevent tumour seeding.

Follow-up was from 7 to 36 months. One operated patient developed early wide-spread multifocal disease throughout the urothelium, including the operated kidney, and died of uraemia. The other three patients have shown no recurrence in the operated kidney, though two have developed recurrences in the bladder or ureter. There have been no track recurrences.

There is a dilemma in the management of upper tract transitional cell carcinoma (TCC): whether to remove the kidney and ureter as the best hope of cure or to be conservative, saving the kidney but risking local recurrence. The dilemma is more acute when there is only one kidney, renal function is poor or the disease is bilateral.

It has been recognised for some years that low grade, low stage upper tract TCC can be treated safely by conservative surgery. Part of the difficulty lies in defining grade and stage before surgery.

We have used the well established techniques of percutaneous renal stone surgery and combined them with local radiotherapy in an approach to some of these problems.

Patients and Methods

Six patients have been either investigated or treated and in each the preliminary approach was the same: the renal collecting system was punctured percutaneously under local anaesthesia. In the first two cases the track was dilated to 22 F and a nephrostomy tube left *in situ* (Fig. 1). At a second procedure, under general anaesthesia, the track was dilated to 26 F and an Amplatz tube passed. We now dilate to 26 F at the first session to avoid the risk of bleeding at the operative session. The interior of the kidney was then inspected using a conventional cystoscope.

Diagnostic group (Table 1A) In two patients with a history of non-invasive bladder TCC a filling defect in a renal pelvis was found on intravenous urography (IVU). In both cases urine cytology was inconclusive and ureteroscopy had proved impossible.

Treatment group (Table 1B) In a further four patients a diagnosis of pelvicaliceal carcinoma was made on the basis of IVU appearances and positive

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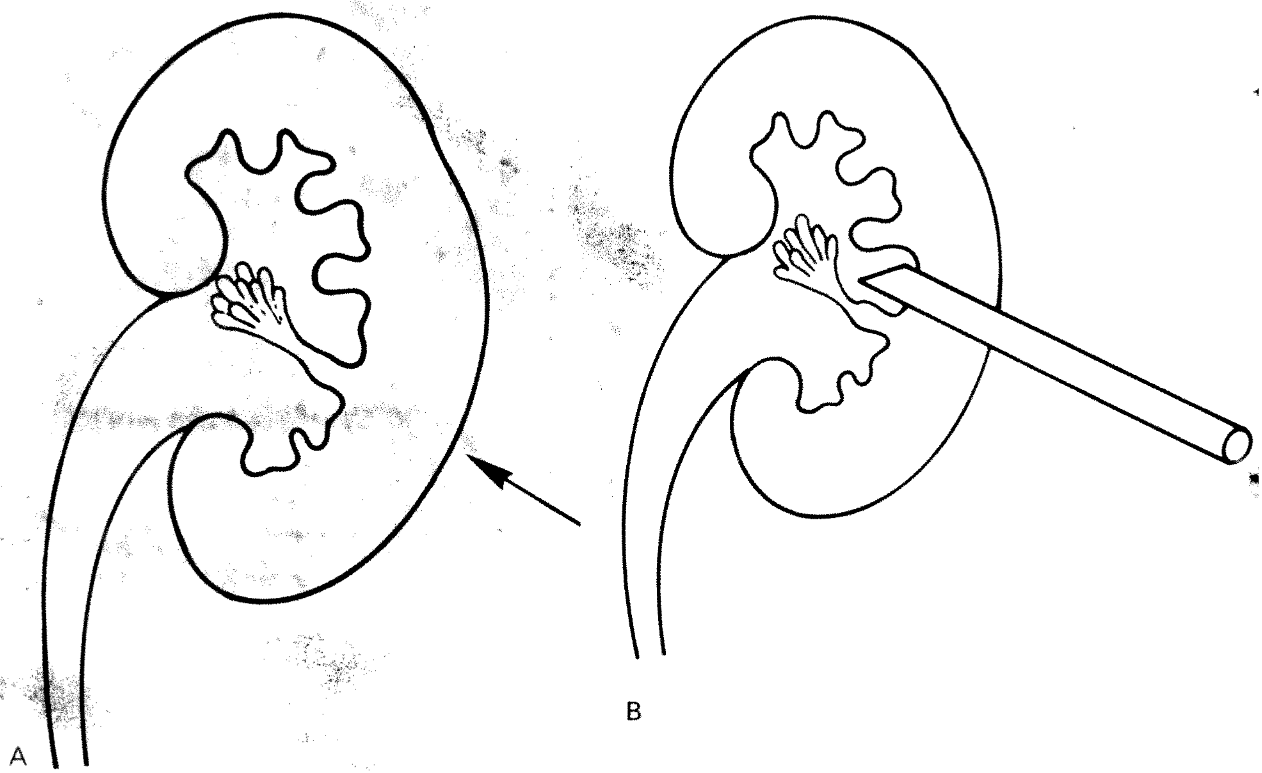

Fig. 1 A. Stage one for diagnostic or surgical procedure. Percutaneous puncture, dilatation of track and nephrostomy tube left in. B. Stage two. 26F Amplatz tube passed, pyeloscopy, biopsies taken, tumour resected or cauterised. Nephrostomy tube left in if tumour was found.

Table 1A Diagnostic Nephroscopy only

Patients	*Age*	*Bladder Ca. Pathology*	*Cytology*	*Nephroscopy*	*Follow-up*
1. R.P.	51	G^1Pta 1966	Suspicious	Normal	32 months
2. L.C.	74	G^1Pta 1980	Suspicious	Stone	15 months

Table 1B Percutaneous Renal Surgery

Patients	*Age*	*Contralateral kidney*	*Tumours in operated kidney*	*Histology*		
				Renal tumour	*Renal random*	*Bladder*
3. A.M.	59	Previous TCC	Ca × 3 cauterised	G_2Px	Ca *in situ*	Ca *in situ*
4. R.B.	64	Clear	Ca × 1 cauterised	G_2Pta	− ve	− ve
5. G.A.	73	Nephrectomy	Ca × 2 resected	G_1Pta	atypia	G_1Pta
6. J.M.	54	Nephrectomy	Ca × 5 cauterised	G_1Pta	hyperplasia	G_1Pta

cytology. Two patients had solitary kidneys because of previous nephrectomy for TCC (one had also had a cystectomy). One patient had had a cystectomy for TCC and a resection of aortic aneurysm; his general health was very poor. The fourth patient had had an open removal of TCC from the same kidney and had a recurrence.

In these patients a percutaneous track was developed in the way already described. At the second stage pyeloscopy was performed. Biopsies were

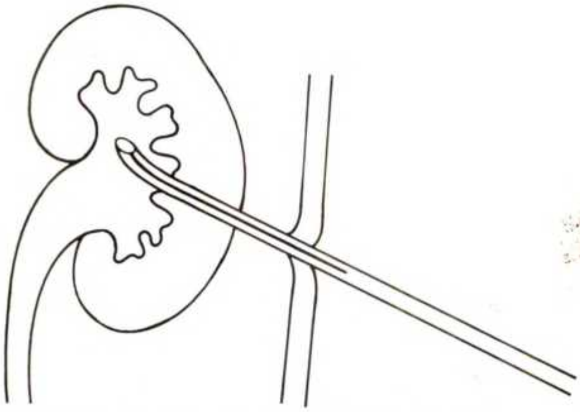

Fig. 2 Diagram of track irradiation for tumour cases.

taken from the tumours and from the pelvic mucosa (Fig. 1B). In three cases the tumours were cauterised.

In the fourth case there was heavy bleeding and the procedure was abandoned. A week later a retrograde catheter was passed to permit irrigation if necessary. The pelvicaliceal system was re-examined through the percutaneous track and multiple tumours were resected without difficulty with a 24 F resectoscope.

At the end of these procedures a 22 F nephrostomy tube was introduced. Between 3 and 8 days later a single radioactive iridium wire was inserted into the nephrostomy tube and fixed with a Spencer-Wells forceps (Fig. 2).

Radioactive iridium (^{192}Ir) has a half life of 74 days and emits gamma rays with a mean energy of 320 KeV. The required length of the wire is generally between 12 and 14 cm. The wire is inserted into the 22 F Porges catheter with 8 mm protruding above the skin surface to ensure an adequate dose to this area. The activity of the wire is approximately equivalent to 1 mg radium/cm. The total dose, at 4 mm radius from the wire, is 4500 cGy and is delivered over 3 to 4 days. The nephrostomy tube and the wire are then removed.

Results

Diagnostic group In the first case a lucent stone, which was the cause of the filling defect, was removed. No other lesion was found. In the second case no lesion was found and the filling defect was thought to be due to a vascular impression. No tumour has developed on follow-up. There were no complications.

Treatment group In all cases a clear view of the pelvicaliceal system was obtained. Random biopsies of the mucosa were taken and the tumours were cleared. The tumours looked exactly as they do when arising in the bladder (Fig. 3) The histological findings are shown in Table 2. After the iridium wire and the nephrostomy tube had been removed the tracks healed without delay and there were no fistulae.

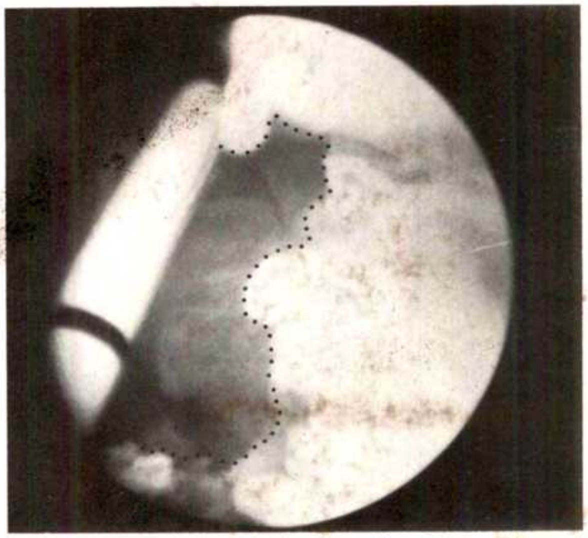

Fig. 3 Endoscopic photograph of a papillary TCC of the renal pelvis. A ureteric catheter has been passed up the ureter. The tumour is marked by the dotted line.

Table 2 Follow-up of Percutaneous Renal Surgery Cases

Patients	*Months*	*Operated kidney*	*General*
A.M.	36	Clear	Ureteric and contralateral recurrence ℞ Interferon Terminal
G.A.	11	Recurrence 10/12	Ureteric recurrence 6/12 ℞ ureterectomy Ileal loop recurrence 10/12 † Uraemia
R.B.	8	Clear	No recurrence anywhere
J.M.	7	Clear	No recurrence except in bladder

Follow-up was from 7 to 36 months. The results are shown in Table 2. In one patient there was, in sequence, recurrence in the ureter, ileal loop and renal pelvis of a solitary system; he died of uraemia. There has been no intra-renal recurrence in the other three patients, though one has a suspicious area remote from the original tumour site (Fig. 4). Two of these three patients have developed recurrences in the bladder and ureter.

The only complication was the intra-operative bleeding already referred to above. There have been no track recurrences.

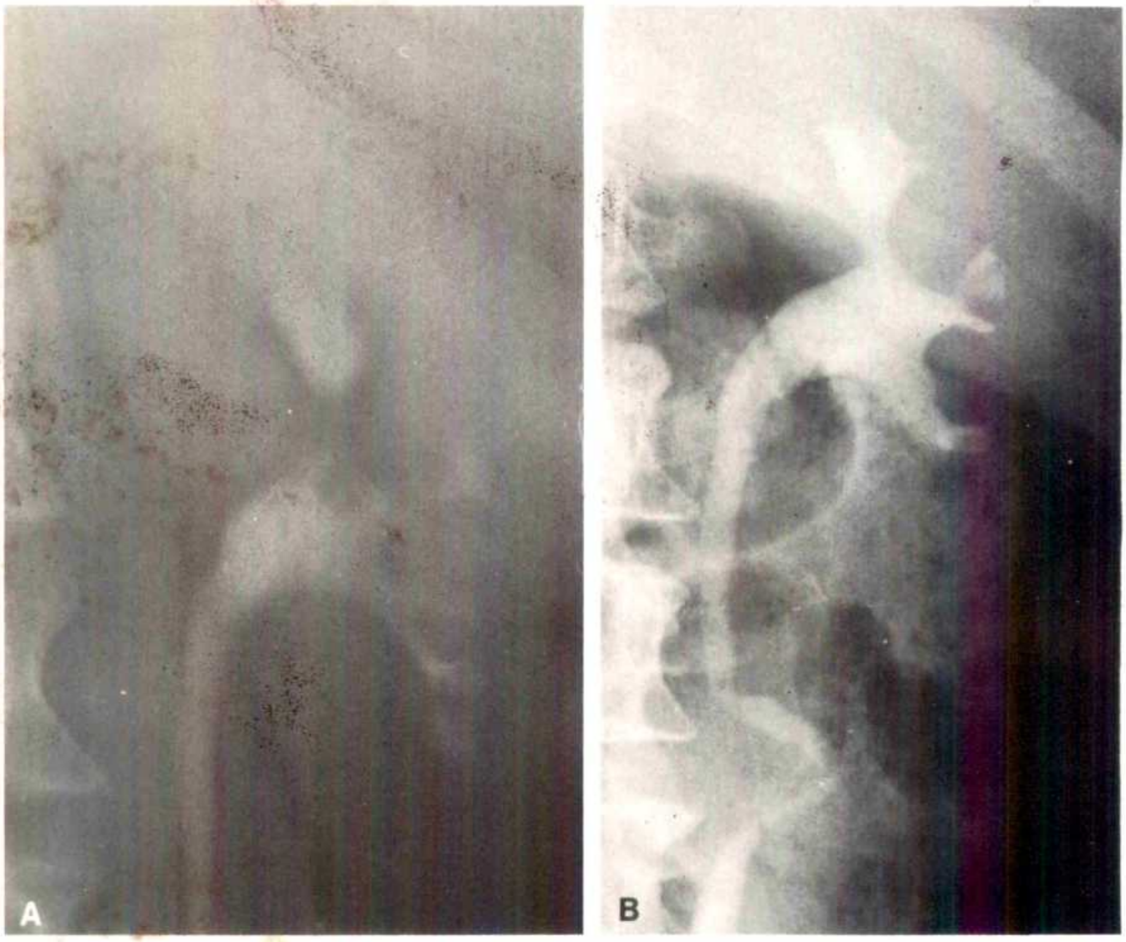

Fig. 4 A. Pre-operative urogram of case 6, showing a TCC of the neck of the upper pole calix. B. The same kidney 7 months post-operatively. There is no tumour recurrence but the non-visualisation of the medial lower pole minor calix is suspicious.

Discussion

Transitional cell carcinoma of the upper urinary tract is an uncommon disease. It is, therefore, not surprising that there is doubt about the best form of management. Most reports are retrospective and it is difficult to deduce the natural history of tumours in different stages and the effect, if any, of treatment.

More effective management would probably be achieved if it were based on accurate staging and grading of tumours, using the same principles as apply to the bladder. For example, no urologist would recommend cystectomy for an isolated non-invasive transitional cell bladder carcinoma. By the same token, a kidney (a more useful organ than the bladder) should not be removed for a single non-invasive carcinoma. However, until recently, nephro-ureterectomy was widely used for all renal TCCs, sometimes with the recognition that the prognosis for non-invasive lesions was better than that for invasive ones (Mazeman, 1976; Cukier *et al.*, 1981; Nocks *et al.*, 1982).

Conservative surgery has been practised in carefully selected cases for many years with good results (Brown and Roumani, 1974; Wallace *et al.*, 1981). A large series has now confirmed the relatively benign course that low grade, low stage disease can follow (Murphy *et al.*, 1980): 5-year survival in this series was exactly that expected for age and sex-matched controls. Metastases from lesions not invading muscle and of grade 1 or 2 have been reported in only 3 of 129 cases regardless of treatment (Grabstald *et al.*, 1971; Batata *et al.*, 1975; Murphy *et al.*, 1980; Nocks *et al.*, 1982). These reports have, no doubt, contributed to the recent cautious recommendation of conservative surgery for low grade, non-invasive disease (Zincke and Neves, 1984). In addition, conservative surgery is indicated for patients with poor renal function, solitary kidneys, Balkan nephropathy and poor general health. Synchronous bilateral disease, which occurs in only 2% of cases (Mazeman, 1976), might be a further indication for a conservative approach.

In this small series we have shown that percutaneous resection or diathermy of intra-renal TCC is feasible. In the short term it has proved safe. The technique can also be used in the grading of upper tract TCC and, especially if combined with computed tomography (Mauro *et al.*, 1982), in disease staging.

Two theoretical, long-term problems exist: pyelovenous back flow carrying tumour cells into the circulation, and percutaneous track implantation. We use a 26 F Amplatz tube and a 24 F or smaller operating instrument. The irrigating bag is kept below 40 cm in height. The irrigating fluid can flow out freely through the Amplatz or down the ureter. The intra-pelvic pressure should not be increased. In an experimental situation it has been shown that pyelovenous back flow does not occur unless the intra-pelvic pressure is raised above 100 cm water (Watson, G. M., personal communication, 1985).

Implantation of tumour cells in the track, leading to local recurrence, should be prevented by local irradiation using radioactive iridium wire which is left in the nephrostomy tube post-operatively to deliver 4500 cGy to the track lining. With open operation for bladder TCC, implantation in the wound was seen only in tumours invading muscle and was prevented by a dose of only 950 cGy given in 3 fractions as pre-operative external beam irradiation (Van der Werf-Messing, 1978).

At present the technique that we have described is suitable for carefully selected cases only. Tumours should be low grade and non-invasive. Patients should be those requiring conservative treatment and unsuitable for other conservative techniques. With more experience, its use could be widened to include most solitary low grade, low stage renal pelvic tumours. Percutaneous endoscopy can also be used for diagnostic examination of the renal collecting system, especially when ureteroscopy has failed.

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The Authors

C. R. J. Woodhouse, FRCS, Consultant Urologist.
M. J. Kellett, FRCR, Consultant Radiologist.
H. J. G. Bloom, MD, FRCP, FRCS, FRCR, Consultant Radiotherapist.

Requests for reprints to: C. R. J. Woodhouse, Academic Unit, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

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Ureteroscopic Pyelolysis for Pelviureteric Junction Obstruction

J. A. INGLIS and D. A. TOLLEY

Department of Urology, Royal Infirmary, Edinburgh

Summary—The development of endourological techniques for the treatment of upper urinary tract disease has concentrated mainly on the endoscopic treatment of upper urinary tract stones. The relief of pelviureteric junction obstruction (PUJ) by percutaneous pyelolysis has recently been reported and the use of the flexible uretero-pyeloscope has also been described. We describe the use of a rigid uretero-renoscope to relieve strictures causing secondary pelviureteric junction obstruction in two cases.

Case 1

A 60-year-old female presented in 1973 with a well differentiated superficial transitional cell carcinoma of the bladder. This was successfully treated by diathermy and subsequent annual check cystoscopy showed no recurrence. An intravenous urogram in 1984 showed a possible filling defect in the right renal pelvis and a poorly functioning left kidney. Right uretero-pyeloscopy showed a papillary transitional cell carcinoma of the renal pelvis. This was resected and treated with intra-pelvic Mitomycin C post-operatively. Check uretero-pyeloscopy 3 months later showed no evidence of recurrent tumour and a left ureteroscopy was carried out. The lower two-thirds of the ureter were normal, but at the level of the pelviureteric junction there was considerable ureteric narrowing. A 4 F ureteric catheter was passed into the renal pelvis under vision and the narrow area within the renal pelvis was divided with a diathermy hook, using the Storz uretero-resectoscope. Pyeloscopy was normal and there was no evidence of tumour. An 8F silicon double-J stent was inserted into the ureter to provide drainage and was left for 2 months. At ureteroscopy, 4 months after removal, there was no evidence of recurrent stricture and the patient remains well and symptom-free.

Case 2

A 46-year-old female had previously undergone three open operations on the left kidney for recurrent stone disease at another hospital. She was referred for percutaneous extraction of a residual stone which appeared to be causing PUJ obstruction (Fig. 1A). A pre-operative DMSA scan showed 12% function from this kidney. A two-stage left percutaneous stone extraction was carried out in August 1984, the stone being disintegrated with ultrasound and all fragments removed. There was considerable oedema of the renal pelvis and it was not possible to identify the PUJ. A check nephrostogram was performed prior to removal of the Cope nephrostomy catheter and this showed evidence of PUJ obstruction (Fig. 1B). It was, therefore, decided to carry out a percutaneous pyelolysis and prior to surgery an attempt was made to pass a 4 F ureteric catheter retrogradely in order to identify the PUJ. The catheter, however, would not pass through the pelviureteric junction and so a rigid ureteroscope was introduced, and the ureteric catheter inserted through the PUJ under vision. Percutaneous pyelolysis was then attempted through the existing nephrostomy track, incising the PUJ posterolaterally, using the Storz urethrotome. A ureteric stent and Cope nephrostomy catheter were left *in situ* but a nephrostogram 5 days later showed the continuing presence of PUJ obstruction due to a narrowed kinked ureter.

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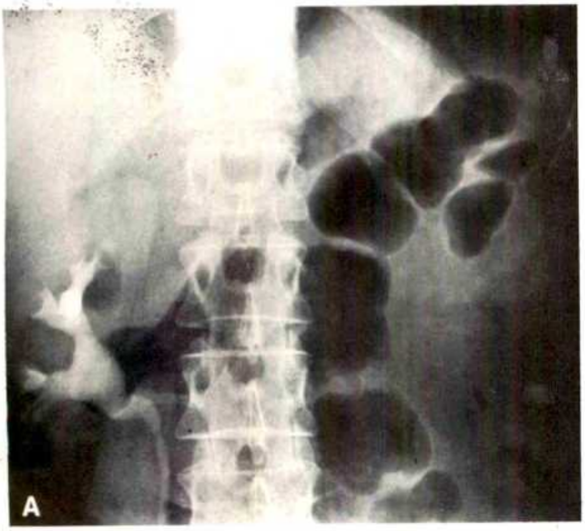

Fig. 1A IVU showing non-functioning left kidney containing renal stone.

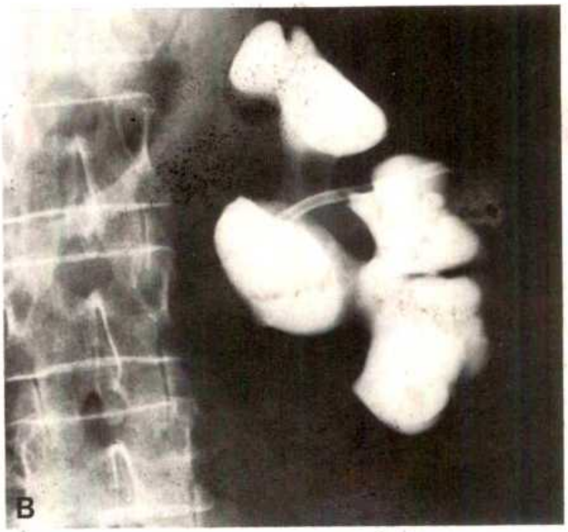

Fig. 1B. Nephrostogram showing PUJ obstruction.

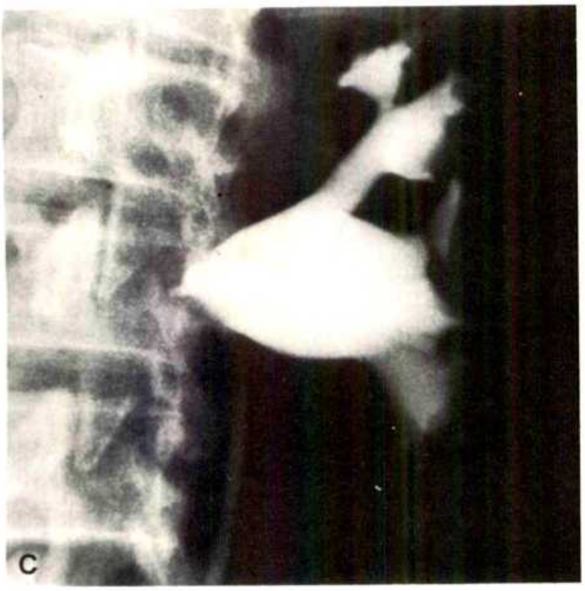

Fig. 1C. Post-operative nephrostogram showing position of Cope catheter and indwelling silicone stent.

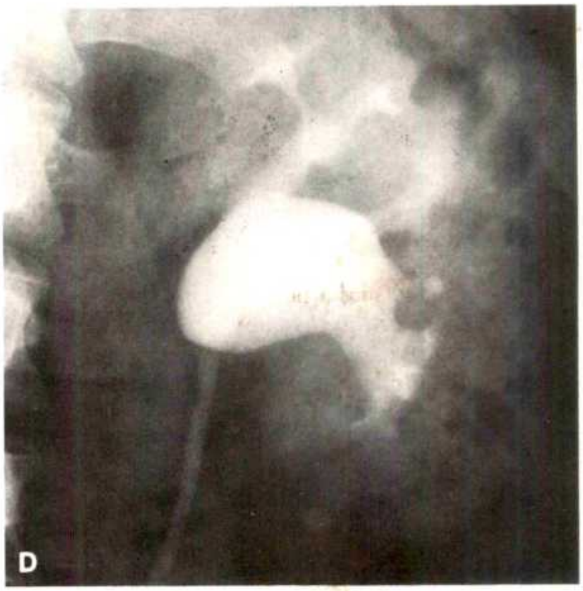

Fig. 1D. IVU at 3 months.

Further ureteroscopy was undertaken with the uretero-resectoscope and on this occasion a diathermy hook was used to perforate the ureter and to make an incision through the extra-ureteric and pelvic fat and into the inferior border of the renal pelvis. This incision was enlarged sufficiently to allow the passage of the uretero-resectoscope into the renal pelvis. An 8 F double-J silicon stent was inserted into the ureter under vision and left *in situ*. A nephrostogram performed 1 week later (Fig. 1C) showed no evidence of leakage and satisfactory drainage from the left kidney and the nephrostomy tube was removed. The stent was removed at cystoscopy 3 months later and the follow-up intravenous urogram showed normal filling of the ureter with satisfactory drainage of the renal pelvis (Fig. 1D). The

DMSA scan has shown an improvement in overall function and the patient remains well, with no pain or urinary infection at 12 months.

Discussion

The rapid advances in endoscopic instrument design herald the need for a revised surgical approach to the management of upper urinary tract disorders. Uretero-renoscopy now has an established role in the diagnosis of upper urinary tract disorders (Tolley and Beynon, 1985) and is widely used for the extraction of ureteric stones (Ford *et al.*, 1983; Tolley and Beynon, 1985).

Interest in the work of Davis (1958), who described the treatment of ureteric strictures with an intubated ureterotomy, has been re-awakened since it became possible to obtain easy percutaneous access to the upper urinary tract. Ramsay *et al.* (1984) recently described the successful treatment of PUJ obstruction by percutaneous pyelolysis. This procedure, however, does involve preliminary cystoscopy and ureteric catheterisation in order to identify the PUJ at pyelolysis. These authors have suggested that if the ureteric catheter cannot be inserted, the procedure will fail. Bagley *et al.* (1985) have reported the combined use of a percutaneous and ureteric approach to PUJ obstruction, passing a rigid instrument percutaneously and using a flexible uretero-pyeloscope introduced retrogradely. This technique, however, requires a separate percutaneous puncture and a longer period of hospitalisation.

A wholly ureteroscopic approach has the advantage that the procedure may be carried out in one stage under general anaesthesia and, provided the procedure is uncomplicated, it could be carried out on an out-patient basis. Furthermore, the technique is essentially the same as for bladder neck incision or incision of a urethral stricture; it is within the scope of every urologist and does not require special skill. Uretero-renoscopy, however, may be a hazardous procedure and difficulties in negotiating the vesico-ureteric junction are occasionally encountered. Furthermore, some difficulty may be encountered in negotiating the pelvic brim, but with care the PUJ may be reached in the vast majority of cases.

In both of the cases described, ureteroscopic pyelolysis has obviated the need for major surgery and almost certain nephrectomy, although follow-up is short. The procedure appears to be associated with little or no morbidity and in selected cases it would appear to be worth attempting ureteroscopic pyelolysis before submitting the patient to major surgery.

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The Authors

J. A. Inglis, FRCS, Urological Registrar.
D. A. Tolley, FRCS, FRCSE, Consultant Urological Surgeon.

Requests for reprints to: D. A. Tolley, Department of Urology, Royal Infirmary, Edinburgh EH3 9YW.

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Analysis of Urinary Calculi Using Photon Induced X-ray Fluorescence (XRF)

R. CESAREO, V. BISCEGLIE, L. J. PEDRAZA, M. GALLUCCI, G. ALPI and F. DI SILVERIO

Department of Biomedical Engineering, University of Rome "La Sapienza", Rome, Italy

Summary—Photon induced X-ray fluorescence has been employed to determine trace elements in urinary calculi. Twenty-one urinary stones, classified in four groups, have been analysed. Besides Ca, elements Fe, Zn and Pb were detected, and Cr and Mn were also detected in some cases.

No clear differences were found between the four groups.

More information is required regarding the pathogenesis of the disease which gives rise to kidney and bladder stones. A study of the composition and structure of stones and their correlation with diet and the composition of urine is of great importance both for treatment and prophylaxis. The homogeneity of the stone's structure (particularly the central area) will provide additional information, which could lead to an understanding of the original formation. Photon induced X-ray fluorescence (XRF) analysis has been used to examine urinary calculi.

XRF analysis is a simple, rapid and non-destructive technique which allows the detection and analysis of major and trace elements in any sample. A photon source is used to excite the inner electrons of the irradiated atoms. Returning to equilibrium, they emit characteristic X-rays, the detection and analysis of which allows the identification and quantification of the elements present. The main advantage of the technique is that it applies to many elements at the same time, in a measuring time of 100-1000 s. Other characteristics vary according to the source of excitation, the specimen, detector and geometrical arrangements, etc. Very low limits of detection can be achieved for elements with the atomic number Z, from about $Z=20$ to $Z=50$, when "infinitely thin" specimens are analysed.

Details of the technique have been given by Cesareo (1982). Very little information is available on trace elements in urinary calculi, but in recent years, the PIXE (proton induced X-ray emission) technique has been used for this purpose (Taylor and Saied, 1982).

Materials and Methods

Preparation of the specimen for XRF analysis is critical, because of the thin sample requirement.

Urinary stones of variable origin, mass and form were grated in different areas with a carborundum file until about 10 to 20 mg of powder were obtained. The powder, mixed with a neutral glue, was deposited on a thin plastic support. The sample was then directly analysed.

An AEG X-ray tube (W-anode) with external interchangeable secondary targets was used to obtain radiation of various energies and high intensity. A typical intensity value of 5.10^8 photons/cm^2 was obtained at the sample position, by employing an Sr-secondary target.

Characteristic X-rays emitted by the sample were detected with a high resolution HPGe-detector (energy resolution 250 eV at 6.4 keV; active area 500 mm^2; thickness 7 mm) connected with a SILENA-1024-pulse height analyser connected to a printer or an XY-plotter.

Results and Discussion

Twenty-one kidney and bladder stones have been

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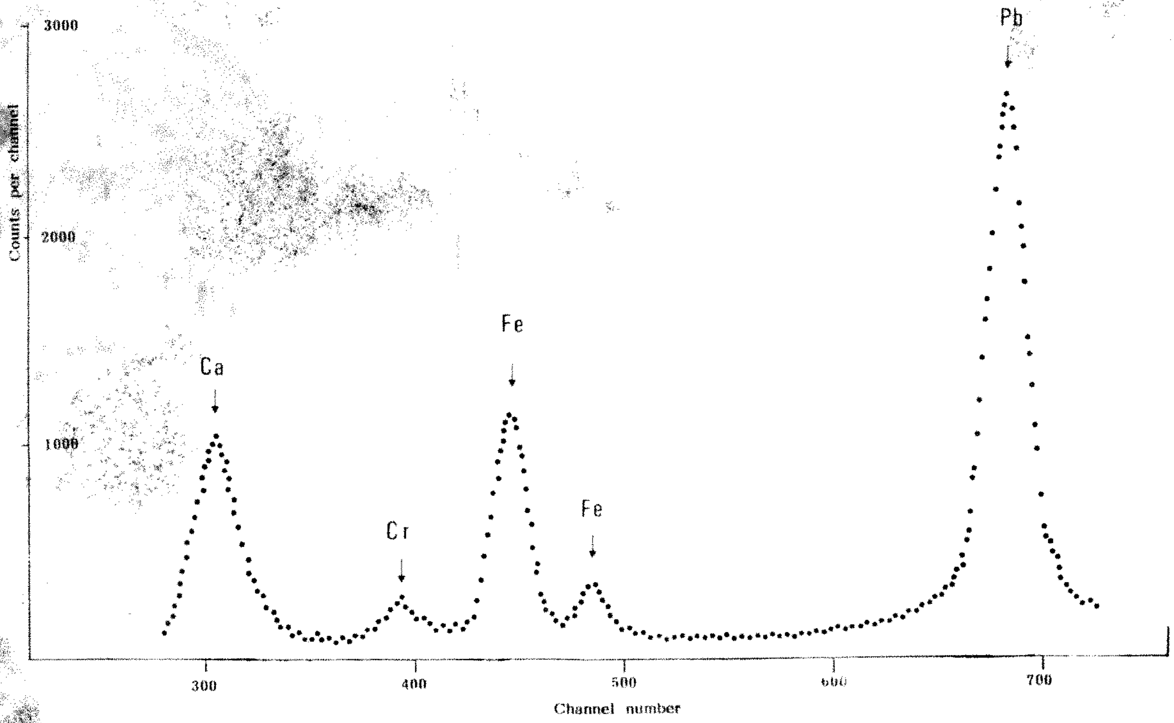

Fig. 1 XRF spectrum of cystine N.1. Secondary target: Sr; measuring time: 500 s.

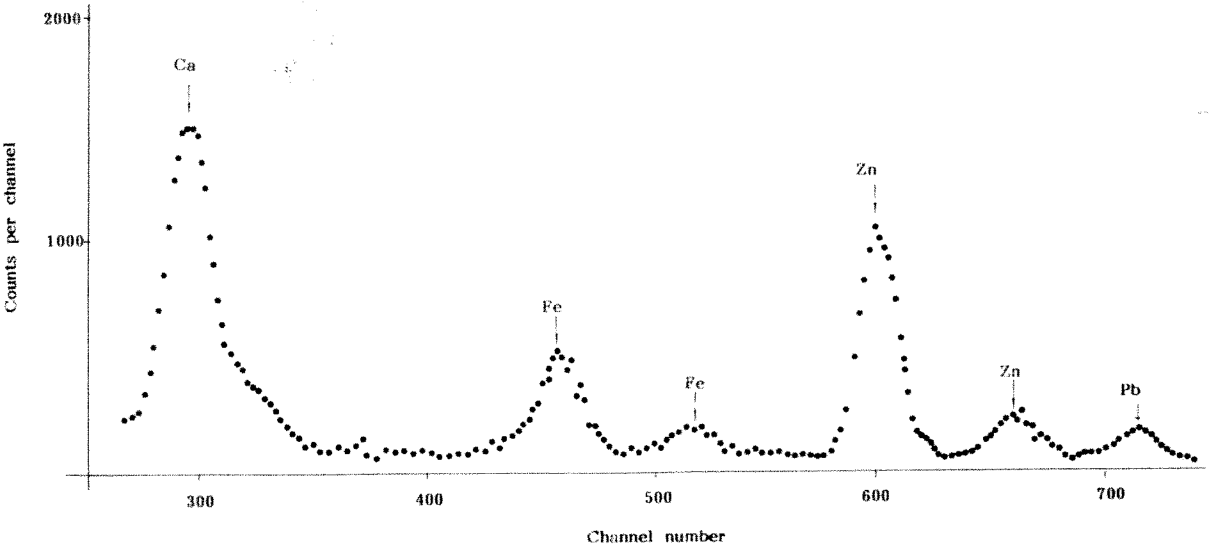

Fig. 2 XRF spectrum of oxalate calculus N.4. Secondary target: Sr; measuring time: 500 s.

analysed. Only stones with a pure composition were selected for XRF analysis (*e.g.* pure calcium oxalate or calcium phosphate stones). Patients with cystine stones were treated with alpha-mercapto-propionyl glycine and alkaline therapy, which has no influence in the trace elements.

Two typical XRF spectra are shown in Figures 1 and 2. The presence of elements Ca, Cr, Fe, Zn and Pb is evident. These results can be compared with those reported by Taylor and Saied (1982), where S, Cl, Ca and Fe were systematically detected and Ag, Ti, Co, Cu, Zn and Pb occasionally. Our

Table Trace elements in 21 urinary calculi by XRF analysis (quantities in μg/g)

	Mn	*Fe*	*Zn*	*Pb*
Cystine calculi N.				
1[*]	0	56	30	12
8	0	0	0	0
13	0	0	0	0
18	0	26	67	42
22	37	0	44	0
24	35	0	89	0
Uric acid N.				
2	0	19	27	0
7	0	25	65	0
9	0	0	0	0
Oxalate calculi N.				
3	0	25	40	1.5
4	0	35	45	2
5	0	45	75	3
19	37	0	11	3.8
25	0	0	5	0
Phosphate calculi N.				
11	0	20	45	2
12	0	19	25	0.5
15	0	0	11	2.5
16	0	0	25	3.5
17	0	0	8	0
20	35	0	7	5
21[*]	0	60	0	95

(*) traces of Cr (see Fig. 1)

apparatus is unable to analyse elements with an atomic number lower than about 20 (calcium) and therefore S and Cl could not be observed. The presence of Ag in the study by Taylor and Saied is remarkable because of the very low content of this element in human tissues and body fluids. The difference in the X spectra could also be due to different diets in various countries.

The Table summarises the quantitative composition (concerning trace elements) of the stones analysed by us. The stones were divided into four groups, according to traditional criteria. No clear difference was noted between the groups and further statistical studies are required. Nevertheless, it can be seen that Zn is present in all oxalate and phosphate stones, with a mean concentration of about 35 and 20 μg/g respectively. Pb is present in almost all oxalate and phosphate stones, with a mean concentration value of about 2 μg/g. The trace elements in cystine and urate calculi were less.

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The Authors

R. Cesareo, MSc, PhD, Professor of Physics, University of Rome.
V. Bisceglie, MSc, Research Student, University of Rome.
L. J. Pedraza, MSc, Research Fellow, International Centre for Theoretical Physics, Trieste.
M. Gallucci, MD, Assistant Professor, Department of Urology, University of Rome.
G. Alpi, MD, Assistant Professor, Department of Urology, University of Rome.
F. Di Silverio, MD, Professor of Urology, University of Rome.

Requests for reprints to: R. Cesareo, Centro per l'Ingegneria Biomedica, Università di Roma "La Sapienza", Palazzo Baleani, Corso Vittorio Emanuele II, 244 00186 Rome, Italy.

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Clinical Significance of Minimal Changes on Intravenous Urography after Spinal Cord Injury

K. V. KUHLEMEIER, L. K. LLOYD and S. L. STOVER

Urology Rehabilitation and Research Center, University of Alabama at Birmingham, Birmingham, USA

Summary—Evidence is given to support the thesis that minimal pyelocaliectasis and ureterectasis are of little clinical significance in spinal cord injured patients. Such renal changes almost always improve or remain stable on sequential examinations. Since moderate or severe pyelocaliectasis is usually detected by renal scintillation procedures, these findings support its use as a urinary tract screening examination along with an abdominal radiograph to detect calculi. The need for long-term serial examination of the urinary tract in spinal cord injury is emphasised.

Since 1977 we have used renal scintigraphy to monitor renal status in spinal cord injured patients. Between 1977 and 1981 most patients were studied both with renal scintigraphy and intravenous urography (IVU) and comparisons of renal status were made between evaluations based on IVU and comprehensive renal scintillation procedures (CRSP). We found early in the study that we could safely eliminate IVU if both the renal scan and IVU were normal the previous year, since renal scintigraphy detected virtually all cases of significant deterioration (Lloyd *et al.*, 1981). In the early stages of the study, however, any patient who showed deterioration of renal status by IVU continued to be tested for follow-up purposes with IVU in addition to CRSP. We present evidence collected to determine if IVU was necessary for follow-up when the previous year's study showed only minimal pyelocaliectasis or ureterectasis. We examined patients with minimal caliceal blunting or ureteric dilatation to see if these conditions persisted, improved or worsened at follow-up. We also correlated IVU status with renal plasma flow, parenchymal thickness and serum creatinine to see if there were significant differences in these indicators of renal status between patients with normal IVUs and those with minimal pyelocaliectasis and ureterectasis.

Patients and Methods

One hundred and fifty-four patients with traumatic spinal cord injury were studied twice, generally 12 months apart. Their renal status was evaluated by renal scintigraphy, IVU, serum creatinine and the presence of urinary tract bacteria. Each IVU was graded separately by a urologist and radiologist for pyelocaliectasis (0 for no caliceal blunting, 1 for minimal, 2 for moderate or 3 for severe caliceal blunting). Kidneys with moderate and severe pyelocaliectasis were grouped together for subsequent statistical analysis because there were very few kidneys with these degrees of pyelocaliectasis. Each IVU was also evaluated for ureterectasis and graded 0 for no ureteric dilatation, 1 for minimal, 2 for moderate or 3 for severe dilatation. If the two graders disagreed as to the grade of pyelocaliectasis or ureterectasis, a physician specialising in physical medicine (physiatrist) adjudicated the disparity. The consensus was then used for analysis. Comprehensive renal scintigraphy procedures, including measurement of effective renal plasma flow (ERPF), were performed as previously described (Tauxe *et al.*, 1980, 1982). The parenchymal thickness of each kidney was measured from IVU tomograms. To remove intergrader variations a physiatrist made all parenchymal thickness measurements. These measurements were made in three locations in each kidney, the upper and lower

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Table 1 Change in Degree of Pyelocaliectasis between Successive Examinations

Kidneys with no change	*Kidneys which worsened*	*Kidneys which improved*
0→0 (193)	0→1 (34)	1→0 (37)
1→1 (19)	0→2,3 (4)	2,3→0 (4)
2,3→2,3 (7)	1→2,3 (7)	2,3→1 (3)

The number preceding the arrow is the initial score for pyelocaliectasis and the number immediately following the arrow is the grade on follow-up examination. The numbers in parentheses are the number of kidneys in that group.

poles and mid-kidney regions, and the three measurements were summed. Serum creatinine levels, urine culture and sensitivity measurements were made by the hospital's clinical laboratory according to their usual procedure.

Results

The pyelocaliectasis grades for the initial and follow-up examinations are given in Table 1. Two hundred and nineteen kidneys had the same degree of pyelocaliectasis on follow-up as on the first examination; 193 had no pyelocaliectasis; 19 had minimal and seven had moderate or severe pyelocaliectasis. Forty-five kidneys worsened between tests. Thirty-four went from no to minimal pyelocaliectasis, four went from no to moderate or severe pyelocaliectasis and seven went from minimal to moderate or severe pyelocaliectasis. Forty-four kidneys showed a decrease in the degree of pyelocaliectasis between the two tests. Minimal pyelocaliectasis disappeared in 37 patients and in seven cases the moderate or severe pyelocaliectasis became minimal (three cases) or disappeared (four cases).

Comparable data for ureterectasis are given in Table 2. Two hundred and fifteen kidneys exhibited no change. Most of these (198) showed no ureterectasis on either test. Fourteen kidneys had minimal ureterectasis on both occasions and only three had moderate or severe ureterectasis on both initial and follow-up examinations. Thirty-seven kidneys without evidence of ureterectasis had minimal ureterectasis on follow-up; five kidneys went from grade 0 to grade 2 or 3 and four kidneys with minimal ureterectasis on the first examination had moderate or severe ureterectasis at follow-up. Forty-six kidneys had less ureterectasis on follow-up; most of these (41) went from minimal to no ureterectasis. One kidney went from moderate to no ureterectasis and four with initial moderate ureterectasis became minimal on follow-up.

Table 2 Change in Degree of Ureterectasis between Successive Examinations

Kidneys with no change	*Kidneys which worsened*	*Kidneys which improved*
0→0 (198)	0→1 (37)	1→0 (41)
1→1 (14)	0→2,3 (5)	2,3→0 (1)
2,3→2,3 (3)	1→2,3 (4)	2,3→1 (4)

See Table 1 for description of data.

Kidneys with no evidence of pyelocaliectasis had a mean ERPF of 246 ml/min (Table 3). This was significantly greater than the ERPF of kidneys with moderate or severe pyelocaliectasis (144 ml/min, $P<0.05$) but not significantly different ($P<0.05$) from the ERPF of kidneys with minimal pyelocaliectasis (233 ml/min). Similarly, the ERPF of kidneys with minimal pyelocaliectasis was greater ($P<0.05$) than that of kidneys with moderate or severe pyelocaliectasis. There were no significant differences in ERPF among the kidneys with the various degrees of ureterectasis ($P>0.05$).

Table 4 shows the relationship between IVU abnormality and renal parenchymal thickness. There were no significant differences in parenchymal thickness among the grades of ureterectasis. The mean parenchymal thickness of kidneys with no evidence of pyelocaliectasis (28.5 mm) was greater ($P<0.05$) than that of kidneys with minimal (25.6 mm) or moderate or severe pyelocaliectasis ($P<0.05$, 22.2 mm). The difference in mean parenchymal thickness between kidneys with minimal pyelocaliectasis and moderate or severe pyelocaliectasis was not significant.

The mean serum creatinine for patients with no pyelocaliectasis or ureterectasis was 0.9 ± 0.2 (SE) mg/dl; the mean and standard errors for patients with minimal pyelocaliectasis or ureterectasis were exactly the same.

Discussion

This study has shown that minor IVU abnormalities are often transient in spinal cord injured patients. Over half of the kidneys (59%) with minimal pyelocaliectasis on the first examination reverted to normal on follow-up. Another 30% of these kidneys with minimal pyelocaliectasis remained so on follow-up. Only seven of 63 kidneys with initial minimal pyelocaliectasis showed subsequent progression. Of 14 kidneys with moderate

Table 3 Relationship between IVU Abnormalities and Effective Renal Plasma Flow

Grade		*Pyelocaliectasis*			*Ureterectasis*	
Normal		246 ml/min			234 ml/min	
			NS			NS
Minimal	$P<0.05$	233		NS	227	
			$P<0.05$			NS
Moderate or severe		144			177	

NS = not statistically significant ($P>0.05$).

Table 4 Relationship between IVU Abnormalities and Parenchymal Thickness

Grade		*Pyelocaliectasis*			*Ureterectasis*	
Normal		28.5 mm			27.6 mm	
			$P<0.05$			NS
Minimal	$P<0.05$	25.6		NS	27.0	
			NS			NS
Moderate or severe		22.2			23.2	

NS = not statistically significant.

pyelocaliectasis initially, seven got better and seven were unchanged. Fifty-nine kidneys had minimal ureteric dilatation at the first examination. Sixty-nine per cent of these had no evidence of ureterectasis on follow-up. Another 24% had no change and only four kidneys (7%) had progression. Even kidneys with moderate or severe ureterectasis were likely to improve; of eight kidneys with moderate or severe ureterectasis initially, five were improved at follow-up. All of these patients had urinary tract infections and most had symptomatic evidence of acute pyelonephritis. The remaining two were unchanged. Thus follow-up of kidneys with minor changes seen on IVU suggests that the changes are of little importance, since these kidneys are likely to improve even without treatment and rarely show progressive deterioration.

The use of IVU as a test of renal function has been reviewed by Banner and Pollock (1980). However, IVU gives primarily anatomical information and by the time anatomical changes are seen, physiological changes may be profound. In this study, evaluation of the functional status of these kidneys as determined by ortho-iodohippurate clearance failed to show significant differences between normal kidneys and those with minimal pyelocaliectasis or ureterectasis. We consider ERPF to be a very sensitive indicator of renal status (Lloyd *et al.*, 1981, 1982; Kuhlemeier *et al.*, 1984b, 1985) and well suited for long-term follow-up of renal function after SCI. The fact that ERPF is not diminished in kidneys with minimal pyelocaliectasis or ureterectasis suggests that minimal IVU changes are of limited clinical significance.

That another commonly used indicator of renal function, serum creatinine, is unaffected by the presence of minimal caliceal blunting or ureteric dilatation is not surprising. It has been firmly established that serum creatinine levels of patients with renal disease are elevated only after functional destruction of a majority of nephrons (Brochner-Mortensen *et al.*, 1977; Rickers *et al.*, 1978). We have examined the use of serum creatinine in monitoring renal function of spinal cord injury patients and have concluded that it is of limited value (Kuhlemeier *et al.*, 1984a).

The precise role of parenchymal thickness as an indicator of renal status is unknown. Hodson and Craven (1966) argued that a generalised decrease in parenchymal thickness was due to urinary tract obstruction, while focal decreases in parenchymal depth were generally due to localised infection. In the present study the parenchymal thickness was not affected by the degree of ureterectasis, a common manifestation of urinary tract obstruction. However, the degree of pyelocaliectasis did have a significant effect on parenchymal thickness, which was significantly greater in kidneys without evidence of pyelocaliectasis than in kidneys with minimal, moderate or severe pyelocaliectasis. In fact, parenchymal thickness was the only parameter in which a significant difference was seen between normal kidneys and those with minimal IVU changes. However, we believe that the absence of functional changes is strong evidence that minimal IVU changes are of only modest clinical significance.

Many urologists believe that ureterectasis in the presence of pyelocaliectasis reflects a more serious condition than ureterectasis alone. This is borne out in the present study, since ureterectasis had no effect on parenchymal thickness, while pyelocaliectasis did have an adverse effect.

Several years ago we began to evaluate the efficacy of CRSP as a screening examination in lieu of IVU and we concluded that CRSP is an effective screening examination and that ERPF is a sensitive measure of renal function (Lloyd *et al.*, 1981, 1982; Kuhlemeier *et al.*, 1985). The aim of the current study was to determine if minimal pyelographic changes, not detected by CRSP, heralded more severe pyelographic abnormalities. Clearly they did not, since such minimal changes were five to ten times as likely to revert to normal on a subsequent examination than to progress to moderate or severe pyelocaliectasis. Furthermore, of 11 kidneys which initially showed normal or minimal change and then had significant progression (to Grade 2 or Grade 3), all but one were detected by CRSP and abdominal radiograph screening examination (Table 5). The sole exception, a female on Foley catheter drainage, had only ureterectasis and on a third examination this had reverted to normal without treatment. The sensitivity of ERPF might permit earlier detection of impending pyelographic abnormalities and we are currently examining patients to see if this might be true.

Some kidneys showed spontaneous improvement from Grade 2 or 3 to 0 or 1 and others improved after a change in bladder management. Appearance of these pyelographic abnormalities (Grade 2 or 3) should prompt a thorough bladder evaluation to determine if urological intervention is needed. Long-term evaluation of spinal injury patients is essential since these abnormalities may occur asymptomatically even many years after the injury. We now use CRSP and abdominal radiography for urinary tract surveillance. A significant decline in ERPF or the appearance of renal calculi then prompts a more thorough evaluation, including IVU and complete bladder functional evaluation. The current study indicates that minor pyelographic abnormalities (Grade 1 pyelocaliectasis or ureterectasis) do not require further investigation, only continued surveillance at yearly intervals.

Table 5 History and Findings in 11 Patients with no or Minimal Pyelocaliectasis or Ureterectasis at Initial Examination and Subsequent Moderate or Severe IVU Abnormalities

Patient No.	*Significant findings*
1	Decreased ERPF. Renal calculi
2	Decreased ERPF. Malnourished. Grade 3 decubiti
3	Decreased ERPF. Grade 3 decubiti
4	Decreased ERPF. Acute pyelonephritis
5	Decreased ERPF. Renal calculi. Multiple UTI with chills and fever
6	Decreased ERPF
7	Decreased ERPF. Renal calculi
8	Decreased ERPF
9	Renal calculi
10	Renal calculi. Multiple UTI, 1 with chills and fever
11	Normal renal scan, no episodes of chills and fever

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The Authors

K. V. Kuhlemeier, PhD, Associate Professor, Department of Rehabilitation Medicine.
L. K. Lloyd, MD, Professor, Division of Urology.
S. L. Stover, MD, Professor and Chairman, Department of Rehabilitation Medicine.

Requests for reprints to: K. V. Kuhlemeier, 547 Spain Rehabilitation Center, University Station, Birmingham, Alabama 35213, USA.

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The Urological Evaluation and Management of Patients with Myelodysplasia

G. D. WEBSTER, A. EL-MAHROUKY, A. R. STONE and C. ZAKRZEWSKI

Division of Urologic Surgery, Duke University Medical Centre, Durham, USA

Summary—The urological evaluation and results of management of 183 myelodysplastic patients are presented. Our management protocol stresses upper tract and infection status surveillance during the early childhood years, and a clean intermittent catheterisation programme with pharmacological manipulation of detrusor and sphincter function as the optimal later management. Continence failures are few and are manageable by sphincter prosthetic surgery or bladder augmentation. Urodynamic results are valuable in children with difficult incontinence or poor upper tracts. The intermittent catheterisation programme reduces the incidence of symptomatic urinary infections in these patients, but the incidence of asymptomatic bacteriuria is high. The adverse results of supravesical diversion in myelodysplastic children rarely justify its use.

The primary goals of urological management in myelodysplasia are the achievement of continence and the prevention of upper urinary tract deterioration and infection. In the past, supravesical urinary diversion was thought appropriate treatment (Smith, 1972) but the introduction of clean intermittent catheterisation, often with neuro-uropharmacological agents, has become the more accepted method (Lapides *et al.*, 1972; Drago *et al.*, 1977; Kyker *et al.*, 1977; Mulcahy *et al.*, 1977; Kass *et al.*, 1979; Plunkett and Braren, 1979). In addition, success with the artificial urinary sphincter and the use of intestinal segments for bladder augmentation have avoided urinary diversion in the small group of patients in whom catheterisation was unsuccessful (Gonzales and Dewolf, 1979; Stone *et al.*, 1984). The introduction of urodynamic techniques has led to better therapy (Blaivas *et al.*, 1977; Light *et al.*, 1984). It has also helped to predict patients likely to develop infection and upper urinary tract deterioration (Diokno *et al.*, 1976; McGuire *et al.*, 1981). Less reliance is now placed on intravenous urography than on renal ultrasound and radionuclide studies.

We discuss the management and results in 183 children with myelodysplasia seen during the past 7 years.

Patients and Methods

One hundred and eighty-three children with myelodysplasia were seen regularly at a multidisciplinary clinic staffed by a urologist, a neurosurgeon, an orthopaedic surgeon, a paediatrician, a psychiatrist and a physical therapist, with access to other specialists if necessary. The children were divided into three groups:

(1) 66 incontinent but otherwise uncomplicated children under 4 years of age in whom upper tract surveillance and avoidance of infections was the primary aim until they were old enough for treatment to achieve continence;

(2) 93 children over 4 years of age in whom attempts were made to achieve continence or complete emptying;

(3) 24 children who had previously undergone supravesical urinary diversion.

At presentation all children underwent upper tract evaluation by intravenous urography and

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renal ultrasound. Cystourethrography and urethral instrumentation were reserved for children with abnormal upper tracts or recurrent infections.

A urodynamic study is now performed at 3 months of age, but for most children in this series it was done at approximately 4 years of age or earlier if the child developed upper tract changes, reflux or recurrent infections. The video-urodynamic study monitored detrusor and sphincter activity during filling, storage and voiding attempts (Webster and Older, 1980). Total bladder pressure, rectal pressure, detrusor pressure, external sphincter electromyography and urine flow rate were measured during these three phases of bladder activity using a six-channel Life-Tech Urolab 1106 and oscilloscope. A Picker fluoroscope hooked up to the urodynamic equipment allowed the simultaneous display of urodynamic and fluoroscopic data on a television monitor. Static urethral pressure profilometry was performed in the supine position. Of the 90 patients (44 males and 46 females) who underwent this evaluation, 89 were managed by a clean intermittent catheterisation (CIC) programme; 12 failed the CIC programme and underwent implantation of an artificial urinary sphincter.

The children in Group 1 wore nappies and were seen every 3 months. At each visit the urine was examined and cultured; the upper tracts were evaluated by renal ultrasound at 6 months, 12 months and 18 months of age and annually thereafter. If the ultrasound was abnormal or the urine infected, intravenous urography was repeated and cystourethrography performed. Radionuclide studies were used particularly in the follow-up of patients with dilated upper tracts, when renal ultrasound and intravenous urography are less useful. Endoscopy was performed only in patients with abnormal parameters in whom surgical intervention was contemplated.

The ages of patients on CIC ranged between 3 months and 22 years (mean 8.4 years). Thirty-five were able to catheterise themselves and their ages ranged from 5 to 22 years (mean 10.9). All patients used a red rubber catheter, between 10 and 12 F. Catheters were washed, not sterilised, and re-used. To achieve continence on a CIC programme, neuro-uropharmacological drugs were prescribed, their type dictated by the urodynamic results (Fig. 1). Ditropan was the usual anticholinergic. Ephedrine or Sudafed was prescribed to increase outlet resistance and imipramine was used in children with a low compliance detrusor. All children on a CIC programme received a single daily dose of a prophylactic antibacterial regardless of infection.

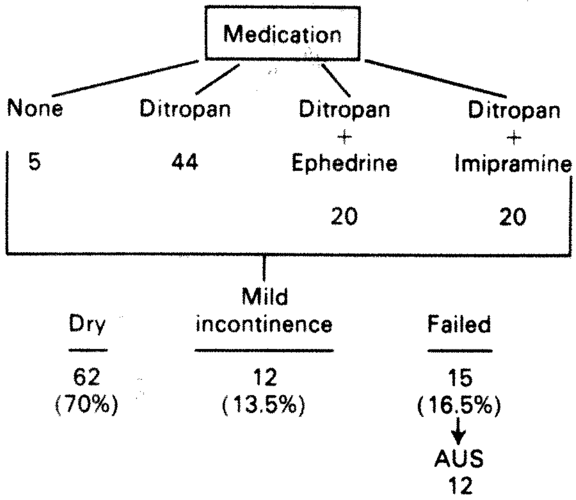

Fig. 1 Eighty-nine patients managed by clean intermittent catheterisation.

Two children underwent cutaneous vesicostomy and three (all with poor upper tracts, low compliance bladders and poor outlet) had supravesical urinary diversion. Their diversions were performed 5 years ago and they would now have been managed by reconstructive techniques. A further 21 patients had undergone supravesical diversion before referral; 11 of these have undergone undiversion and are now managed by CIC. Cystoplasty was required in most of those patients being undiverted.

Results

The 66 children in Group 1 will be given the appropriate treatment to achieve continence when they are about 4 years old. Nineteen have had isolated infections and are on daily antibiotic prophylaxis. The need to change management (because of abnormal parameters) in 12 children in this group persuaded us to perform urodynamic evaluation on the younger children.

Of the 90 children undergoing video-urodynamic study (Fig. 2) we found detrusor hyper-reflexia in 56 (62%) and detrusor areflexia in 34 (38%). Thirty patients in the latter group had low compliance with high terminal filling pressures (Fig. 3). Striated sphincter denervation was evident in 62 patients (69%), detrusor sphincter dyssynergia in 14 (15%) and an apparently innervated but non-relaxing sphincter in 14. Detrusor and sphincter function assessed urodynamically did not always correlate with the apparent neurological lesion

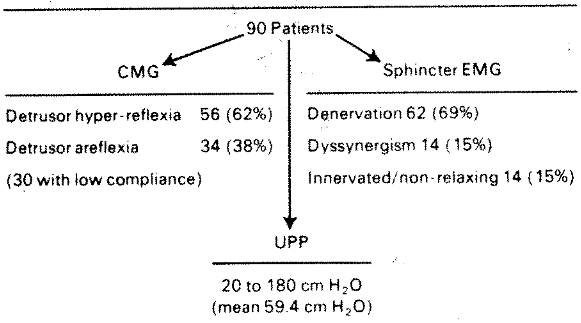

Fig. 2 Urodynamic results.

(Light *et al.*, 1984). Static urethral pressure profiles were obtained in 71 cases. Urethral closing pressure ranged from 20 to 180 cm H_2O (mean 59.4 cm H_2O). Efficient emptying was rarely achieved during the micturition study because no child could generate voluntary contractions and voiding was accomplished by the Valsalva or Credé manoeuvre. Efficient emptying was required and achieved in the group receiving artificial urinary sphincters, although two required an external sphincterotomy before implantation.

Sixty-two of the 89 patients managed by CIC are dry. Twelve have episodes of incontinence which rarely occur more than once daily and require a panty liner. Fifteen were considered failures; 12 of these were given artificial urinary sphincters and are now continent. The degree of continence did not depend on whether the patient was ambulatory or confined to a wheelchair.

Upper tracts were normal at the institution of the CIC programme in 56 cases and in none did upper tract deterioration ensue. Vesicoureteric reflux was present in 17 patients, but following alteration in bladder dynamics by CIC plus medication it improved in 12 and reimplantation was performed in only three.

Before commencing the CIC programme, 52 of 77 patients (68%) had symptomatic urinary tract infections, 7 (9%) had experienced asymptomatic bacteriuria and only 30 (39%) entered the programme with no history of infection (Table). Following the catheterisation programme the incidence of symptomatic urinary infections was markedly reduced and occurred in only 14 patients (15%), but 78 (87%) remained asymptomatically bacteriuric. None of the patients entering the catheterisation programme with no history of infection developed symptomatic infections but 13 developed asymptomatic bacteriuria.

Of five patients who had undergone supravesical urinary diversion because of upper tract deterioration and intractable incontinence, none showed improvement in their upper tracts and two had further deterioration. Of the 19 patients diverted for urinary incontinence alone, all had had normal upper tracts before surgery but five subsequently developed ureteropyelocaliectasis and cortical scarring. Sixteen patients with ileal loops had chronic bacteriuria and two developed recurrent episodes of symptomatic pyelonephritis. Of those patients whose upper tracts deteriorated after supravesical diversion, ureteroileal anastomotic obstruction was the cause in two, and this necessitated surgical revision of the anastomosis. Stomal stenosis requiring revision occurred in three cases.

Discussion

Our results indicate that the myelodysplastic patient can usually be managed by conservative treatment. Urinary continence, the goal usually uppermost in the patient's mind, is achievable in 83.5% of cases using a CIC programme and medication alone, although considerable manipulation of medication is necessary to achieve good results. Those who fail this programme may do so because of low outlet resistance, in which case artificial urinary sphincter surgery has proven successful in 12 cases. In females, outlet resistance may be augmented by fascial sling cystourethrography. Other failures may be caused by intractable detrusor hyper-reflexia or a low compliance bladder, for both of which conditions augmentation cystoplasty may be appropriate. The high incidence of low compliance amongst the areflexic bladders is surprising. We found that this group of patients responded particularly well to Ditropan plus imipramine. Far less impressive was the success of ephedrine in improving continence in those in whom low outlet resistance was the predominant problem.

The use of prophylactic antibacterial therapy in patients on clean intermittent catheterisation is controversial (Cass, 1976; Anderson, 1980), but few will argue against its need in patients with reflux or symptomatic urinary infections. Our results indicate a marked decrease in the incidence of symptomatic urinary infections in patients placed on a CIC programme and given antibiotic prophylaxis. No patient who was previously uninfected developed symptomatic infections on the CIC programme, but the incidence of asymptomatic bacteriuria was high. Intravesical pressure events may impair bladder defence mechanisms by caus-

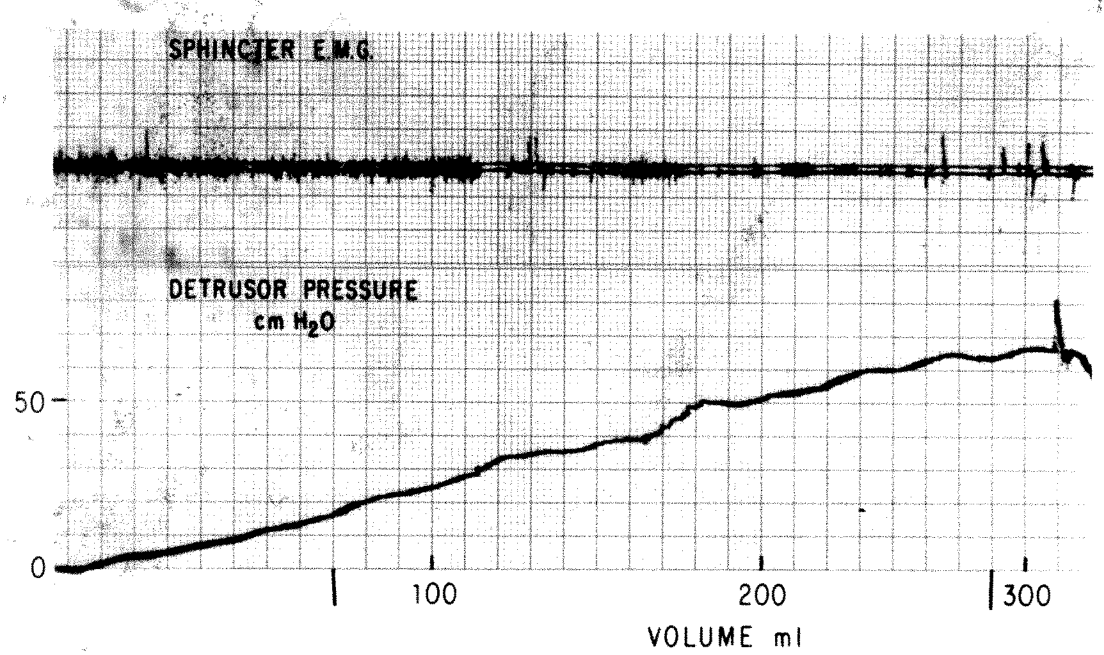

Fig. 3 Combined cystometrogram and sphincter electromyogram in myelodysplastic child with intractable incontinence despite pharmacological manipulation and CIC. The low compliance detrusor is evident with a terminal filling pressure of 66 cm H_2O at a capacity of 300 ml. Denervation of the striated sphincter is implied by the sparse activity on the EMG tracing and was confirmed on the oscilloscope. The child ultimately underwent bladder augmentation and artificial urinary sphincter implantation.

Table Infection Status of 77 Patients Managed by CIC

	Before CIC	*After CIC*
Symptomatic UTIs	52* (58%)	14* (15%)
Asymptomatic bacteriuria	7* (8%)	78* (87%)
Sterile urine	30 (34%)	11 (12%)

* (Some bacteriuric patients also had symptomatic UTIs)

ing mucosal ischaemia, and pharmacological manipulation to decrease detrusor activity is used even when it is not entirely necessary to achieve continence. Complete bladder emptying at the time of catheterisation is a most important preventative measure and is stressed when teaching the programme (Hinman, 1977).

We have found video-urodynamic studies invaluable for the investigation of the patient who fails to achieve continence and for the patient with upper tract deterioration. Cystometry to predict detrusor behaviour and striated sphincter electromyography with urethral pressure profilometry to predict outlet activity were the most valuable studies. We used to delay urodynamic studies until an age when continence became necessary, except in children who showed upper tract radiographic changes, but now we perform these studies as soon after the neonatal period as is feasible (McGuire *et al.*, 1981). The urodynamic findings which indicate a need for more careful surveillance or immediate institution of a catheterisation programme are the hyper-reflexic dyssynergically obstructed system and the low detrusor compliance with a high urethral closing pressure. However, early institution of a catheterisation programme generally requires pharmacological manipulation and the drugs available are not well tolerated by the young child.

Our results confirm that upper tract deterioration may take place after uncomplicated ileal loop urinary diversion (Pitts and Mueke, 1979), and 5 of the 19 patients diverted for urinary incontinence alone developed ureteropyelocaliectasis. Pitts and Muecke (1979) showed that 11% of renal units showed damage following supravesical diversion and that the risk increased with time. The need for urinary diversion in patients with neurogenic bladder dysfunction is confined to the rare patient with devastated upper and lower urinary tract anatomy in whom continence cannot be achieved. The majority of children previously diverted are now candidates for undiversion either to their own bladder, managed by pharmacological manipulation and CIC, or to a bladder augmented by enterocystoplasty techniques. The outlet problem is usually manageable by artificial urinary sphincter or a fascial sling. Young children with upper tract deterioration who do not respond to intermittent catheterisation, or in whom a CIC programme is not possible because of urethral size, are best managed initially by cutaneous vesicostomy until they are big enough for reconstructive procedures.

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The Authors

G. D. Webster, FRCSE, Assistant Professor.
A. El-Mahrouky, MD, Fellow.
A. R. Stone, FRCSE, Fellow.
C. Zakrzewski, PA-C, Physician's Assistant.

Requests for reprints to: G. D. Webster, Box 3146, Duke University Medical Center, Durham, North Carolina 27710, USA.

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Ileocaecocystoplasty in Urinary Tract Reconstruction in Children

E. WESPES, A. R. STONE and L. R. KING

Division of Urology, Department of Surgery, Duke University Medical Centre, Durham, USA

Summary—Ten children have undergone lower urinary tract reconstruction by ileocaecocystoplasty. Four patients had previously been diverted and the other six were reconstructed because of intractable incontinence or deteriorating renal function. Continence was primarily achieved in eight patients and renal function improved or remained stable in all 10. Reflux was prevented by a plicated ileocaecal valve in five of eight patients. Continued pharmacological manipulation, intermittent self catheterisation and secondary surgical intervention were frequently necessary in these patients who required careful counselling and follow-up.

The treatment of children presenting with severe dysfunction of the lower urinary tract has changed dramatically in recent years. Permanent external conduit urinary diversion is now rare because of the development of effective drug treatment for incontinence, acceptance of intermittent catheterisation as an alternative to diversion, and the realisation that a high proportion of children treated by permanent diversion develop significant long-term complications (Bauer *et al.*, 1980; Brendler and Stephenson, 1981). External conduit diversion will provide decompression in children with severe obstruction of the upper urinary tract but stomal problems, stenosis and urinary tract infection often lead to progressive renal deterioration and stone formation in later years (Gittes, 1977). These considerations have led to the increased use of intestinal segments to reconstruct the defective urinary tract (Hensle *et al.*, 1982; Stone *et al.*, 1982; Whitmore and Gittes, 1983).

The successful outcome of lower urinary tract reconstruction has also been enhanced by the use of drugs to reduce bladder hyper-reflexia and to improve sphincter tone. Intermittent catheterisation may then be required to improve continence and minimise the risk of infection (Lapides *et al.*, 1976).

We recount our experience with the use of ileocaecal cystoplasty in reconstructing the abnormal lower urinary tract in children with neurogenic or anatomical abnormalities.

Patients and Methods

Over a 2-year period 10 patients aged 4 to 15 years (mean 9½ years; 5 males and 5 females) underwent an ileocaecocystoplasty for undiversion or primary urinary tract reconstruction. The original diagnosis and treatment before the ileocaecocystoplasty are shown in the Table.

Initially, Gastrografin (Schering Pharmaceuticals) or barium enemas were performed pre-operatively to see whether the ileocaecal valve appeared competent at relatively high intracolic pressures. This proved to be unreliable as two patients who demonstrated competence of the ileocaecal valve pre-operatively refluxed across the valve after their reconstruction.

Urodynamic evaluation was carried out pre-operatively in all patients to characterise urethrovesical behaviour. Bladder capacity, detrusor compliance, the amplitude of any unstable contractions and the urethral pressure profile were recorded. However, pre-operative urodynamic assessment does not necessarily allow one to predict with certainty the way the vesicourethral unit will behave following reconstruction. Patients are always

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Table Patients' Original Diseases and Treatment Before Ileocaecocystoplasty

Patient	*Age*	*Sex*	*Original disease*	*Treatment before ICC*
J.S.	9	M	Myelomeningocele	Ileal conduit (Fig. 3)
T.C.	14	F	Ureteric reflux associated with urethrovesical dyssynergia	Ureteric reimplantation→failure→transuretero-ureterostomy
A.A.	4	M	Non-compliant bladder due to posterior urethral valve	Valve resection
G.G.	11	F	Solitary right kidney with ureteral ectopia; tiny bladder	Ileal ureter
G.B.	10	M	Posterior urethral valve	Resection of the valve. Ureteric reimplantation→failure→transuretero-ureterostomy with ureterostomy
C.G.	12	F	Solitary left kidney; ectopic ureter	Ureterostomy (Fig. 4)
G.D.	9	F	Reflux	Reimplantation→failure→second reimplantation→failure
D.P.	15	F	Non-neurogenic neurogenic bladder syndrome with ureteric reflux	Reimplantation→failure (×2) (Fig. 2)
I.R.	9	M	Myelomeningocele	Right ureteric reimplantation→failure→second right reimplantation→failure
A.C.	12	M	Sacral agenesis	Ileal conduit

taught intermittent catheterisation pre-operatively. A percutaneous cystostomy tube may be introduced pre-operatively and sterile fluid instilled in order to assess bladder capacity and any degree of incontinence. Poor outflow resistance makes it more likely that an artificial sphincter may eventually be required for continence. However, the urethral pressure profile is not always accurate in this regard and so we seldom implant an artificial sphincter at the time of undiversion or reconstruction and we did not do so in the patients reported herein.

When reflux is absent, the patient who is to undergo undiversion is evaluated by retrograde urography to assess the length of the ureteric stumps pre-operatively, since reconstruction of the urinary tract is often better accomplished with re-anastomosis of the "native" ureters when this is feasible. If, however, this option is present but the defunctionalised bladder will not expand, or is poorly compliant, we usually choose reconstruction by caecocystoplasty, anastomosing the ureters to the terminal ileum above the ileocaecal valve instead of uretero-ureterostomy and cystoplasty with an isolated sigmoid or small bowel segment. These are, however, viable alternatives in management.

Our preferred technique of ileocaecocystoplasty involves supratrigonal cystectomy, leaving a generous disc of trigone for anastomosis to the right colon. If the ureters drain well and do not reflux, the ureterovesical junctions are preserved. Otherwise, ureteric stumps are excised and the ureters are anastomosed to the terminal ileum behind the plicated ileocaecal valve.

Via a midline incision the right colon, caecum and terminal ileum are mobilised with their blood supply based on the ileocolic artery and vein. As long as these vessels are preserved, the isolated ileocolic segment can be rotated freely at least 180° after it has been detached from the rest of the intestinal tract. Ileal length is adapted to the length of remaining proximal ureter. After bowel continuity has been restored, the ileocaecal segment is rotated inferiorly as the caecum is advanced into the pelvis.

In undiversion, the proximal end of an existing ileal conduit with intact and mature uretero-ileal anastomoses can often be preserved. The conduit is detached from the abdominal wall, shortened by resecting the distal portion, and anastomosed end-to-end to the terminal ileum.

At operation, sterile fluid is infused by gravity into the caecum and the pressure at which the fluid refluxes across the ileocaecal valve into the ileum is estimated. The valve is then plicated with interrupted silk sutures to prevent reflux at pressures lower than 80 cm H_2O. The ileal segment is then infused to ascertain that flow across the plicated valve is unimpeded. The initial capacity of the caecum and right colonic segment to be used in this reconstruction is approximately 300 ml, representing about 20 cm of caecum and ascending colon.

After the ileocaecal valve has been strengthened, the terminal ileum can also be led around the dome of the rotated caecum in the Gittes antireflux manoeuvre, suturing the terminal ileum to the adjacent adventitia of the caecum with interrupted silk sutures.

All of the bladder above the trigone is then

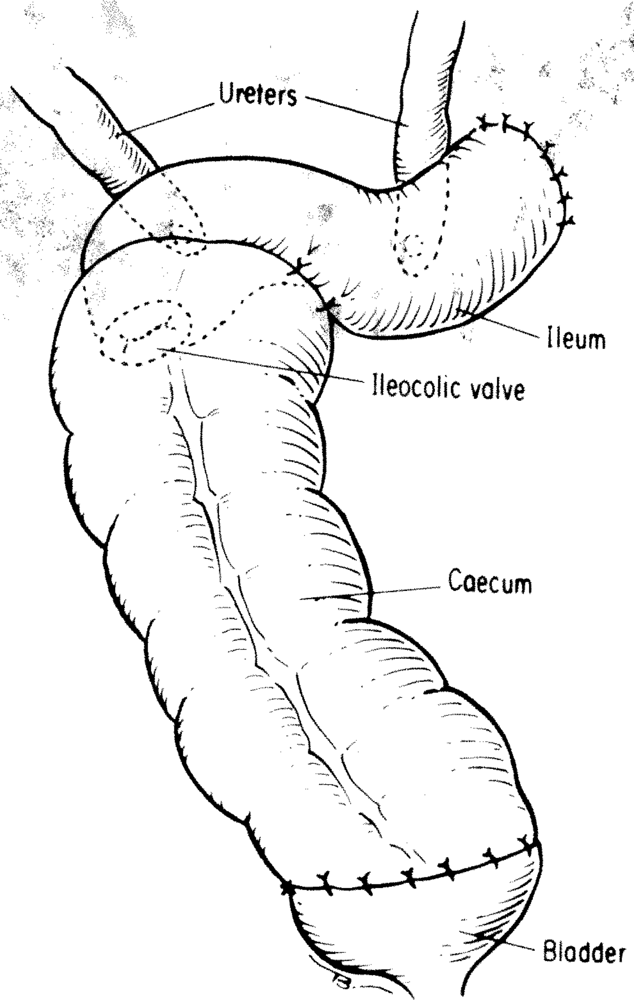

Fig. 1 The isolated ileocaecal segment is anastomosed to the bladder base with two layers of chromic catgut after subtotal cystectomy. The ileocaecal valve has been plicated with non-absorbable sutures to prevent reflux back into the ileum at pressures below 89 cm H_2O. The ureters are implanted into the ileum, or the proximal end of the existing ileal conduit is attached. The ileum may then be sewn to the dome of the caecum to diminish further the risk of reflux.

removed, leaving the bladder base intact as described above. Cautery reduces bleeding and speeds this portion of the procedure. A two-layer anastomosis is begun between the adventitia of the posterior caecal segment and the adventitia of the posterior bladder base, followed by full thickness running sutures between the edges of the caecum and the bladder muscle and mucosa. The lateral and anterior aspects of the anastomosis are then buttressed with adventitial sutures. A suprapubic tube is placed in the caecum before it is completely closed (Fig. 1).

In one patient the ureters were unobstructed and reflux was absent, so they were left in place at the bladder base; in another patient a Leadbetter-type ureterocaecal anastomosis was performed using the caecum only for reconstruction. In eight cases the ureters were implanted into the ileum behind the plicated ileocaecal valve as described above.

A unilateral nephrostomy is used after ileocaecal plication. When the ureters have been implanted into the terminal ileum above the ileocaecal valve, one nephrostomy will drain both kidneys. The nephrostomy is kept in place until free drainage across the plicated ileocaecal valve is demonstrated by measuring the renal pelvic pressure.

Results

Two patients developed obstruction of the plicated

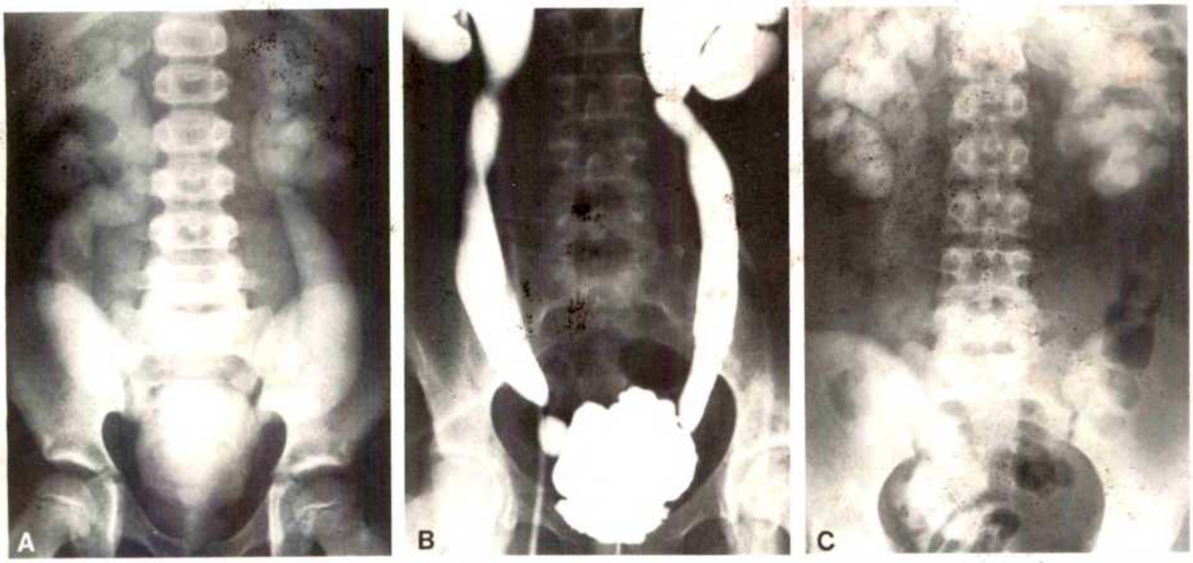

Fig. 2 A. IVU in 1975 of 10-year-old girl with reflux and obstruction. B. Cystogram in 1982, after two failed reimplants. The non-compliant bladder, which may have been a part of the original problem, predisposing the ureteric reimplantations to complications, is now obvious. The patient had repeatedly refused diversion, and the creatinine was around 3 mg%. C. Cystogram after double voiding. The patient catheterises herself twice a day to eliminate residual urine and prevent infection. Voiding is otherwise normal and the creatinine has settled at 2.3-2.5 mg%.

ileocaecal valve and needed prolonged nephrostomy drainage. One obstruction resolved spontaneously and the other required surgical revision.

Renal function remained stable or improved in all patients.

Urine cultures have usually been negative, apart from two patients who exhibit chronic asymptomatic bacteriuria.

Eight patients were primarily continent after ileocaecocystoplasty. Five of these use intermittent catheterisation combined with pharmacological treatment with anticholinergics, ephedrine or imipramine. One patient required a Scott sphincter because of persistent wetting and poor outflow resistance, and another is often still wet, but has adequate sphincter resistance, and is dry when adhering to a strict regime of timed voiding. An artificial sphincter may, however, be required in this patient.

When the ureters were reimplanted into the ileum, reflux was prevented in five instances, but occurred in two early patients in whom a competent ileocaecal valve on Gastrografin enema was not plicated and in one patient who subsequently developed reflux across a plicated valve.

Discussion

Intestinal segments have been used to reconstruct the urinary tract since the turn of the century and numerous modifications have been made since then (Cibert, 1953; Couvelaire, 1955; Grégoir, 1958; Gil Vernet, 1960; Cibert and Cibert, 1962; Küss *et al.*, 1970; Hendren, 1973; Gittes, 1977; Turner Warwick, 1979). Over the past 15 years, the number of children treated by external diversion has diminished dramatically. Children with neuropathic bladder can now usually be managed by intermittent catheterisation and/or pharmacological manipulation, but some will remain incontinent or show increasing renal deterioration. Substitution of a portion of the abnormal non-compliant detrusor with bowel will usually provide a more manageable, functional bladder. Similarly, children with anatomical abnormalities of the lower urinary tract, such as urethral valves or ureterovesical reflux, may need to be treated in this manner when bladder pressure remains abnormally high despite sophisticated anticholinergic therapy.

In undiversion, the selection of patients is of paramount importance. The patients needs to be motivated and be willing to accept a major operation to restore the urinary tract. Since the possibilities of undiversion are now widely known amongst this patient population, it is best if the patient requests information about the feasibility of the procedure. Alternatively, when we see a patient with a problem such as stomal stenosis, we mention the

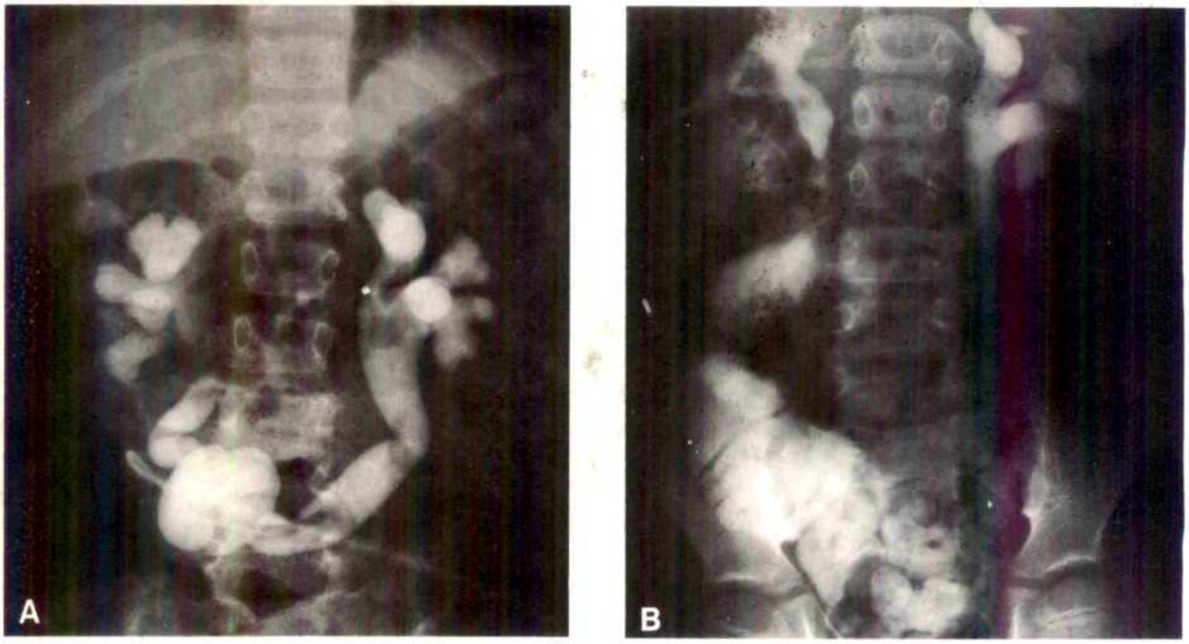

Fig. 3 A. IVU in 1982 on boy with myelodysplasia. An ileal conduit was performed in 1977 and he now has stomal stenosis. B. Undiversion was accomplished by subtotal cystectomy and caecocystoplasty. The ileocaecal valve was plicated at surgery with non-absorbable sutures to withstand a pressure of 80 cm H_2O before reflux into the ileum occurred. Patient has no post-operative reflux and is dry on intermittent catheterisation every 3 to 5 h and ephedrine 25 mg 3 times a day. The serum creatinine has remained normal.

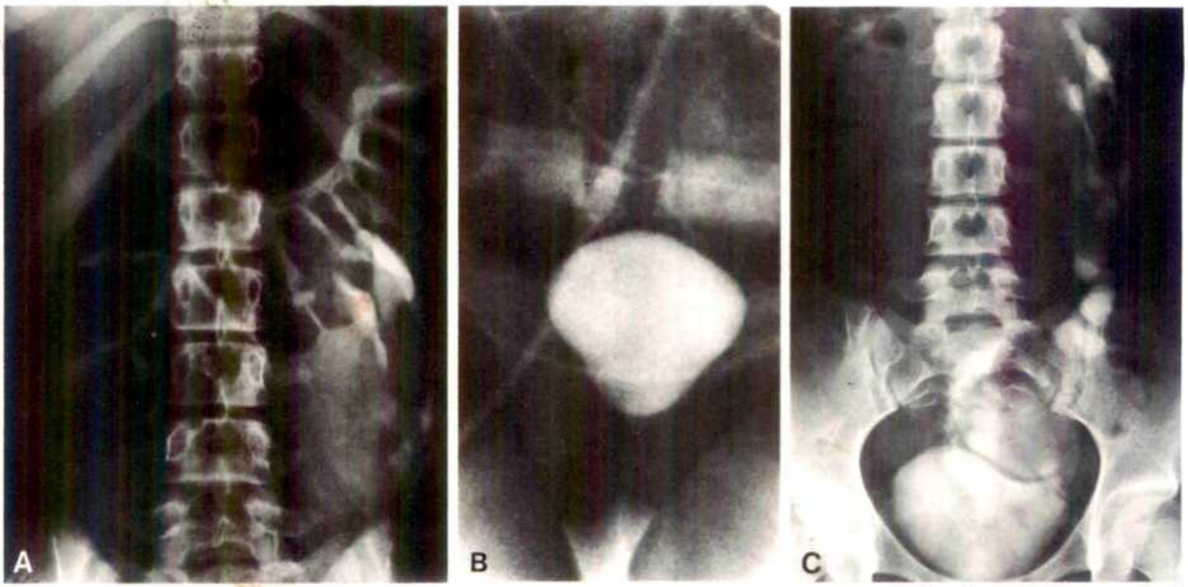

Fig. 4 A. IVU in 14-year-old girl with a single ectopic ureter treated by loop ureterostomy at 2 months of age. B. The tiny, 15-ml bladder did not expand with cyclic filling over a 3-week trial period. Undiversion was therefore carried out by ileocaecal cystoplasty, using a 13-cm segment of terminal ileum to make up ureteric length. C. IVU 9 months after surgery. Note the re-expansion of the bladder. Urinary control is normal, as is the serum creatinine.

possibility of urinary tract reconstruction as an alternative to a simple stomal revision. If an operation is required, most patients choose to be undiverted. However, many children in adolescence who have a supravesical diversion that is functioning satisfactorily will elect to continue with this and avoid further major surgery. We feel this is often a healthy attitude, especially when the patient is well adjusted to the diversion and appliance.

In general, when cystoplasty is chosen, the choice of the intestinal segment to be used is open to discussion. At present it seems to depend more on the preference of the particular surgeon than the specific characteristics of the bowel segment (Gittes, 1977). Even though the peristaltic characteristics of ileum, caecum and sigmoid colon are not entirely similar, there are as yet no objective data to dictate preferential use of one or the other segment (Grégoir, 1958). In general, we prefer to use sigmoid colon when a ureter of near normal calibre is to be implanted into the bowel segment by an antirefluxing technique. We usually prefer a Leadbetter type of anastomosis in this situation, as the muscle of the sigmoid is thicker than in the caecum and is also smoother, permitting easier development of the buttressing muscle flaps. We have not yet used an antireflux anastomosis to the small bowel, though the results of the Camey procedure using ileum to replace the bladder suggest that this may be feasible (Lilien and Camey, 1984).

An ileocaecocystoplasty is preferred for many of our young patients because of the great mobility of this segment when it is isolated from the intestinal tract based on the ileocaecal artery. In addition, the ileocaecal valve is attractive for use as the antireflux mechanism (Smith and Hinman, 1955). It may be plicated or intussuscepted to prevent vesicoureteric reflux. We are currently experimenting with intussusception and anastomosis of the full thickness of the outer wall of the intussusceptum to the back wall of the caecum in order to hold the intussuscepted segment in place. The terminal ileum can also be used to replace any loss of ureteric length.

In our series, two patients with a plicated ileal caecal valve had prolonged obstruction at this site, probably due to post-operative oedema. For this reason we use nephrostomy drainage whenever possible because the nephrostomy can be left in place until free drainage of urine into the augmented bladder can be demonstrated, and it also provides access for balloon dilation of the ileocaecal valve, which has been used successfully in one instance. One patient required open revision of the plication before upper tract pressures fell to normal.

Although it is important to characterise vesicourethral function urodynamically, this assessment does not necessarily predict continence after reconstruction (Kogan and Levitt, 1977). We feel this information is essential, however, in selecting the technique to be used and in counselling the patient on the probable results of reconstruction and any further management that may be required.

Failure to remove most of the abnormal detrusor can occasionally have an unfavourable effect. Anastomotic stenosis may occur, causing the augmentation to function more like a diverticulum than a functional detrusor. This predisposes to urinary infection and may also result in failure to reduce unstable bladder contractions and intravesical pressure.

Post-operative incontinence has not been a frequent problem, but in two patients, one of whom required a sphincter, it was accurately predicted by the pre-operative urodynamic investigations and we were prepared for this problem. Lesser degrees of incontinence can usually be overcome by the use of anticholinergics or ephedrine. Intermittent catheterisation is often used since the reconstructed detrusor may not empty efficiently alone (Lapides *et al.*, 1976; Turner Warwick, 1979; Green *et al.*, 1983).

Patients who dislike the idea of intermittent catheterisation pre-operatively currently represent a contraindication to undiversion, as we are unable to predict with certainty whether this will be needed after the reconstruction (Whitmore and Gittes, 1983).

Mucus secretion rarely causes a problem after the immediate post-operative period, when it may plug cystostomy tubes or catheters. The amount of mucus produced by the bowel segment seems to decline with time as long as emptying of the bladder is efficient (Stone *et al.*, 1982).

In general, renal function should remain stable or improve following reduction of high intravesical pressures, correction of reflux and prevention of urinary infection. There is much debate as to whether patients with severe impairment of renal function are suitable for undiversion. However, there is often no suitable alternative therapy available, and the reconstructed urinary tract is more easily able to accept a transplanted kidney than a suboptimal diversion or an abnormal detrusor (Hensle *et al.*, 1982).

It is concluded that ileocaecocystoplasty is useful as a means of undiversion in carefully selected children and for bladder substitution in treating poorly compliant detrusors which are resistant to drug treatment. The poorly compliant bladder is usually due to neuropathic bladder, the non-neurogenic neurogenic bladder syndrome, the thickened fibrotic bladder persisting after resection of urethral valves, and it is occasionally seen in the otherwise normal patient who has undergone multiple bladder operations. It is often unclear whether the bladder instability or hyper-reflexia is the result of surgery or was the cause of the original urological problem. Ileocaecocystoplasty requires commitment on the part of both patient and urologist to continuing follow-up, and the patient must be willing to accept the possibility of the need for an artificial sphincter device or intermittent catheterisation in order to achieve satisfactory continence.

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The Authors

E. Wespes, MD, Resident.

A. R. Stone, MD, FRCS, Chief Resident.

L. R. King, MD, Professor of Urology and Head of Section of Paediatric Urology.

Requests for reprints to: E. Wespes, Cliniques Universitaires de Bruxelles, Hôpital Erasme, 808 route de Lennik, 1070 Brussels, Belgium.

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Analysis of the Pattern of Urine Loss in Women with Incontinence as Measured by Weighing Perineal Pads

J. R. SUTHERST, M. C. BROWN and D. RICHMOND

Department of Obstetrics and Gynaecology and Institute of Medical and Dental Bioengineering, University of Liverpool, Liverpool

Summary—Three hundred and thirty-five women with urinary incontinence underwent a pad-weighing test for quantifying urine loss. Each one wore a series of pre-weighed sanitary towels for a total of 1 h. The pads were weighed again after use. The test results gave information about the severity of the incontinence which was not easy to obtain either from patient interview or from clinical examination. The type of activity was the main factor determining urine loss, although patients with detrusor instability lost more on average than the others. Voiding during the test period did not appear to influence the overall test results. Reproducibility of the test has been studied in 50 patients.

In 1981 we described a simple method for assessing the severity of incontinence in women (Sutherst *et al.*, 1981). It had been stated earlier that the actual amount of urine leakage should be measured because clinical interview and examination by themselves can provide only subjective information (Stanton and Ritchie, 1977). Furthermore, leakage is sometimes not demonstrable when a patient is being examined and therefore its amount at other times can only be guessed.

Since then others have reported their experience of similar tests (Klarskov and Hald, 1983; Christensen *et al.*, 1984; Eadie *et al.*, 1984; Mundt-Petterssen *et al.*, 1984; Versi and Cardozo, 1984). It is difficult to interpret the results of some of these reports because the numbers of patients studied were small.

We present here the results of pad-weighing in 335 consecutive female patients seen between 1981 and 1984. The same method was used throughout.

Patients and Methods

Each patient referred to our incontinence clinic was instructed to empty her bladder and then drink 1 litre of fluid (orange juice) as quickly as possible. She was given six sanitary towels and was instructed to wear each one for 10 min. The first pad was put on approximately 1 h after she had started to drink the fluid. During the next hour she was asked to perform a series of exercises which we thought might cause leakage of urine. Each pad was weighed before and after use on a beam balance which had a recording accuracy of 0.1 g. The exercise programme which has been found to be acceptable to the patients referred to our unit is as follows:

(i) Walking round the ward.
(ii) Bed making.
(iii) Picking up objects from the floor.
(iv) Spending several minutes hand washing at a sink.
(v) Climbing up and down stairs.
(vi) Walking up and down steps carrying a heavy bag.

This pad-weighing test was used in 335 consecutive women (no menstruating women were included in the study). The weight changes in each patient's pads were plotted on an incontinence chart (Fig. 1) together with the volume voided on completion of the test and the amount of any urine voided during the test (though patients were encouraged not to void during the test period). Each patient was asked whether she felt the

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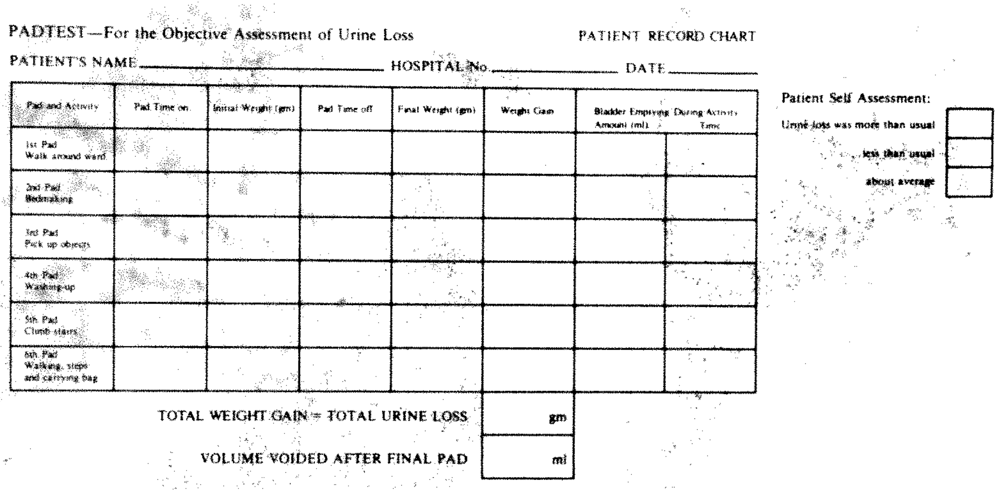

PADTEST—For the Objective Assessment of Urine Loss PATIENT RECORD CHART

PATIENT'S NAME ________ HOSPITAL No. ________ DATE ________

Pad and Activity	Pad Time on	Initial Weight (gm)	Pad Time off	Final Weight (gm)	Weight Gain	Bladder Emptying During Activity Amount (ml)	Time
1st Pad Walk around ward							
2nd Pad Bedmaking							
3rd Pad Pick up objects							
4th Pad Washing-up							
5th Pad Climb stairs							
6th Pad Walking, steps and carrying bag							

TOTAL WEIGHT GAIN = TOTAL URINE LOSS ☐ gm

VOLUME VOIDED AFTER FINAL PAD ☐ ml

Patient Self Assessment:

Urine loss was more than usual ☐

less than usual ☐

about average ☐

Fig. 1 Incontinence chart on which pad weight changes are recorded.

amount of leakage which occurred was usual for her, or more or less than usual.

The mean age of the women was 48 years (range 20-82) and mean parity 3 (range 0-13); 286 patients complained of stress incontinence, 237 of urge incontinence and 212 of a mixture of the two. Seventeen did not complain of incontinence, whilst 63 leaked without any warning or provocation and 67 wet the bed at night. In 206 the symptoms were bad enough for them to wear protective clothing or a pad all the time. In 111 the leakage was said to be continuous, in 137 only occasional and in the remainder somewhere between the two. One hundred and twenty-three said that they leaked large volumes of urine (similar to voiding), 195 that the urine came away in short spurts and 119 that leakage occurred even when the bladder had been recently emptied.

Urinary leakage was seen during clinical examination in only 117 patients. The diagnosis reported after full investigation was: genuine stress incontinence (GSI), 171 patients; detrusor instability (DI), 52 patients; mixed GSI and DI, 35 patients; other diagnoses, 53 patients. In 24 no urodynamic abnormality was detected.

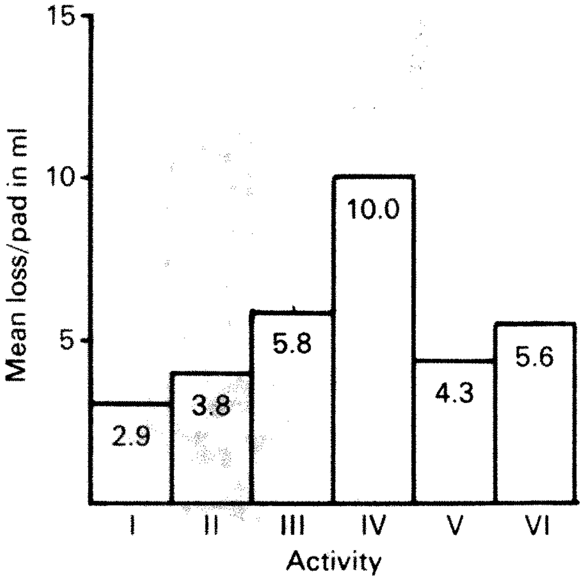

Fig. 2 Mean loss per pad against activity in 355 female patients.

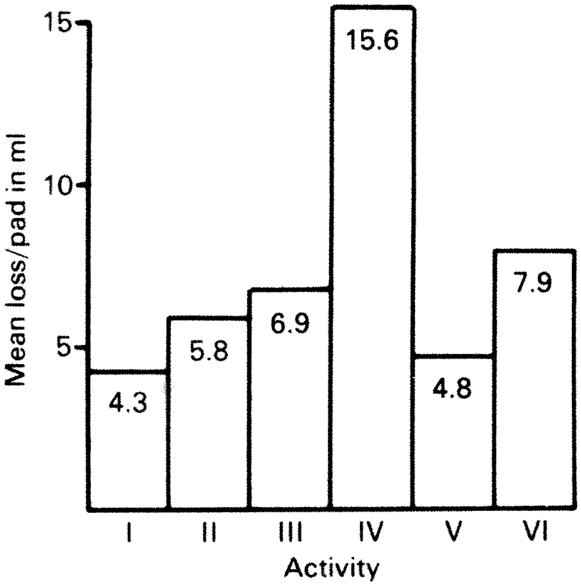

Fig. 3 Mean loss per pad against activity in 87 women with detrusor instability.

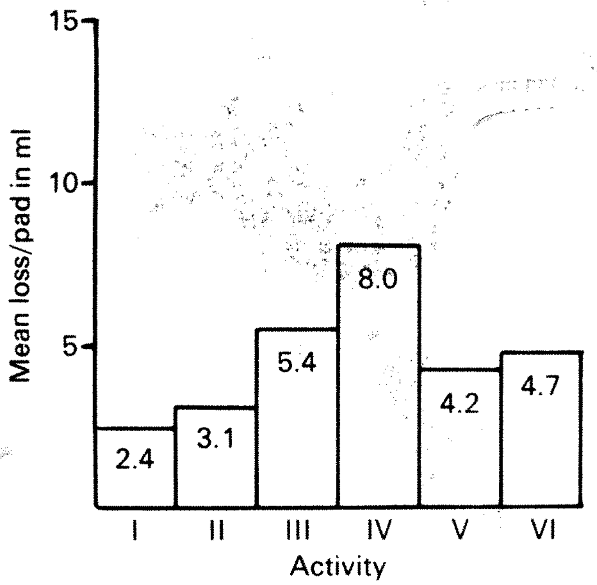

Fig. 4 Mean loss per pad against activity in 248 women without detrusor instability.

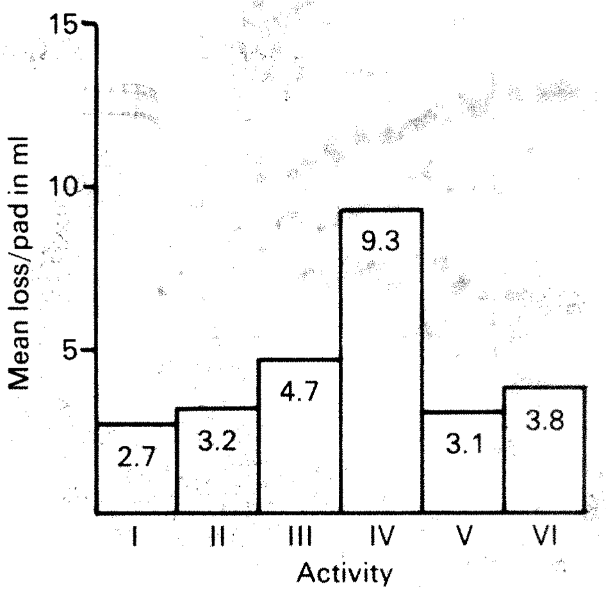

Fig. 5 Mean loss per pad against activity in 177 women who voided during the test.

Results

In 253 women (75%) the pad weight increase was greater than 1 g/h (range 0-401.1) and in 82 (25%) was less than 1 g/h. Our previous work showed that in 95% (mean +2SD) of 50 normal women the total weight gain was less than 1 g over the whole hour (Sutherst *et al.*, 1981). The same figure for 49 normal women was quoted by Versi and Cardozo (1984). Therefore, any pad weight change equal to or greater than 1 g was taken to indicate incontinence.

The pattern of urine loss

The pattern of urine loss in the whole group of 335 patients is shown in Figure 2.

Originally we thought that the pattern of urine loss was diagnostic. Women with detrusor instability appeared to leak large quantities into one or two pads (Fig. 3). By contrast, women with genuine stress incontinence seemed to lose small amounts into each of the pads (Fig. 4).Experience has shown that the pattern of urine loss can be the same in both. However, women with detrusor instability did leak more on average than those with sphincter weakness alone (43.5 ml and 37 ml respectively).

Table Average total pad loss vs patients' age

Age	*No. of patients*	*Pad loss*
20–29	18	17.4
30–39	70	20.5
40–49	104	29.3
50–59	76	29.8
60–69	43	47.2
70–79	23	72.5
80–89	1	53.7

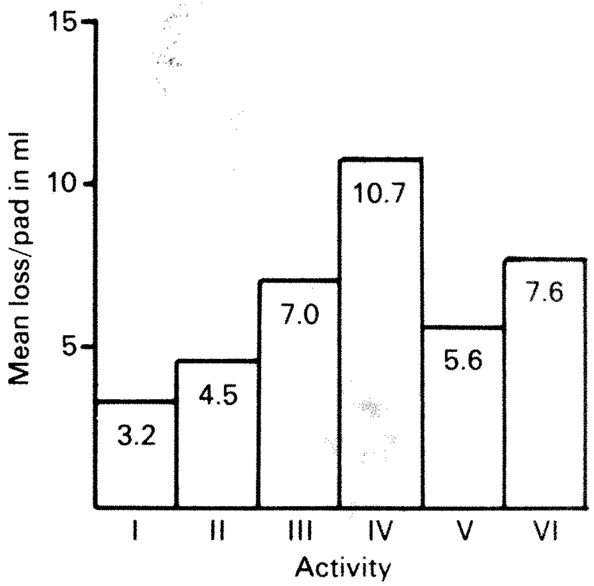

Fig. 6 Mean loss per pad against activity in 158 women who did not void during the test.

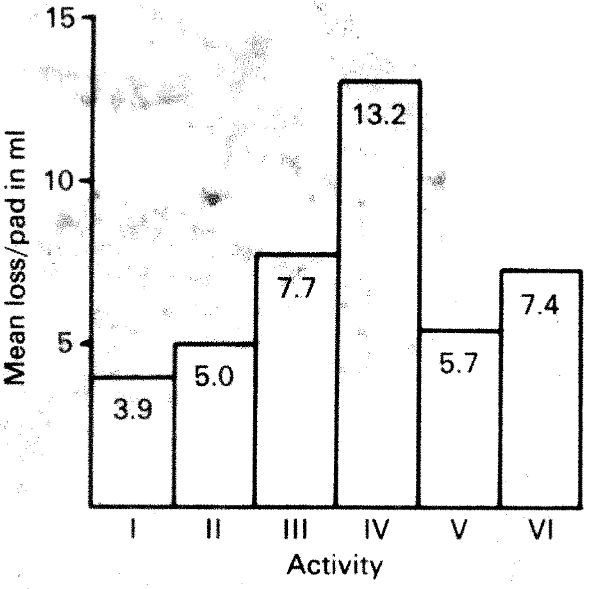

Fig. 7 Mean loss per pad against activity in 253 incontinent patients.

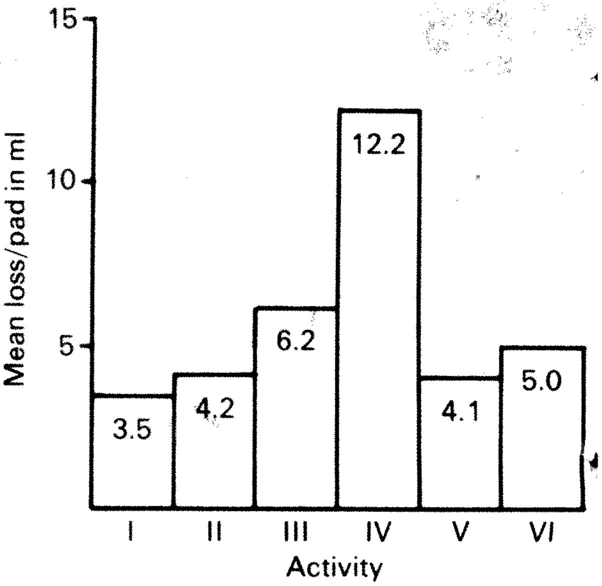

Fig. 9 Mean loss per pad against activity in 134 incontinent women who voided during the test.

The relationship between urine loss and age

The average total pad loss against age is shown in the Table. The greatest number of patients was in the 40 to 49 age group, but women aged between 70 and 79 leaked most on average (72.5 ml/h).

The effect of voiding during the test

One hundred and seventy-seven women needed to void during the test period and 158 did not. The average urine losses against activity in each of these groups are shown in Figures 5 and 6.

Of the women who voided, 134 (76%) were identified by the test as being wet and 43 (24%) dry. Of the ones who did not void, 119 (75%) were shown to be wet and 39 (25%) dry. The average losses in all of the patients identified as being incontinent and the average losses in voiders and non-voiders amongst these incontinent patients are plotted against exercises in Figures 7 to 9.

It can be seen that the pattern of urine loss is the same in all groups. Furthermore, the percentage of patients identified as being wet and dry in both voiding and non-voiding groups was the same (Fig. 10). This suggests that voiding during the test makes little or no difference to the overall test result. This finding is at variance with findings in other reports (open discussion during International Continence Society meeting, Aachen, 1983).

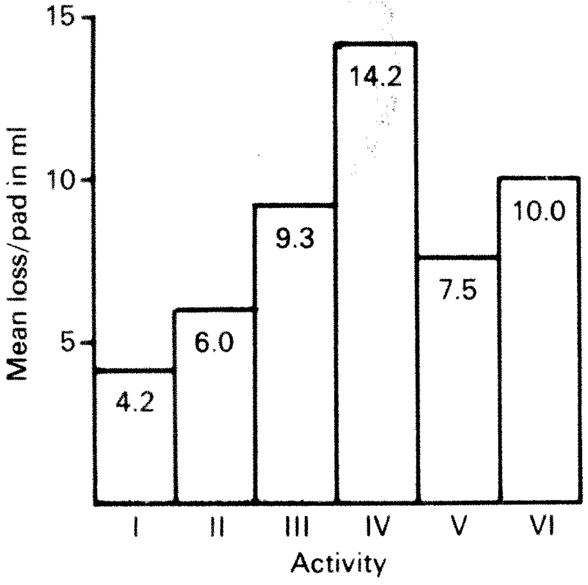

Fig. 8 Mean loss per pad against activity in 119 incontinent women who did not void during the test.

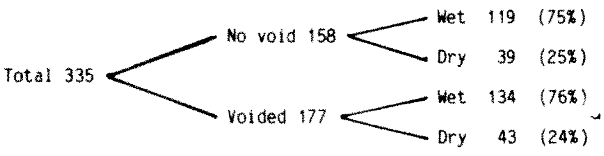

Fig. 10 Proportions of patients identified as either wet or dry in women who voided during the test period and those who did not.

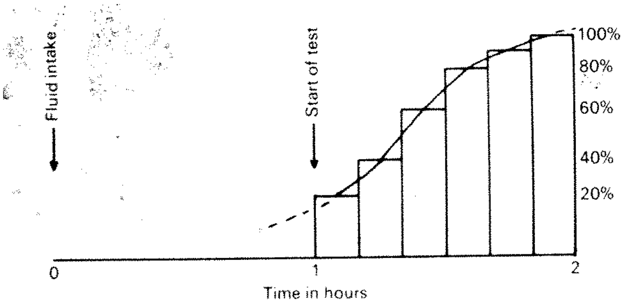

Fig. 11 Identification of incontinence against time (or number of pads).

The identification of incontinence related to the length of the test

In our test there is a waiting period of approximately 1 h between the intake of fluid and the start of the exercises/activities. We designed the test in this way in the hope that a substantial diuresis would be under way when the exercise programme began. The number of wet patients (those having a pad weight change of more than 1 g by the end of the test period) is plotted against time (number of pads) in Figure 11.

The shape of the graph suggests that a test beginning before a diuresis is under way may miss a fair number of patients, but that prolonging the test beyond 2 h from fluid intake to the end of the test would not yield many more.

Discussion

The vulval pad-weighing method of quantifying urine loss in women with incontinence is easy to perform and is non-invasive. The apparatus required is commonly available and the information provided is easy to understand. The extent of pad weight change which we accept as normal matches that of other investigators (Versi and Cardozo, 1984).

We adopted a programme of voiding followed by the intake of a large volume of fluid in order to standardise (as far as possible) the amount of urine in the patient's bladder without having to catheterise her. The plan was that this should be a test suitable for any clinic, where catheterisation facilities were not necessarily available.

After the method was first described by Sutherst *et al.* (1981), the International Continence Society established a working party to study alternative (but similar) tests which might be more applicable to a wider range of incontinent patients. The final design has not yet been decided, though the need for such a test has been accepted. It has even been said that this investigation is the "bottom line" test for any centre specialising in urodynamic investigation (Stephenson, 1984; personal communication). However, some favour a shorter test period which is less demanding on their and their patients' time, others question the accuracy and reproducibility of pad-weighing and others have recommended variations in the exercise regimen and the amount of fluid intake at the start of the test. In particular, voiding during the test has been said to invalidate the results (open discussion during International Continence Society meetings, 1983 and 1984).

The published results of variations on the theme are open to criticism. Klarskov and Hald (1983) studied only 50 patients in a 60-min test and although they concluded that reproducibility was satisfactory, this part of their report was on only 19 patients. Versi and Cardozo (1984) reported their experience of the test in only 36 incontinent patients and Eadie *et al.* (1984), Christensen *et al.* (1984) and Mundt-Petterssen *et al.* (1984) in only 30, 20 and 20 patients respectively.

We have used this test in our own department now for 5 years and have come to accept that large numbers of patients are needed before any universally acceptable format can be described. Clearly the exercise regimen is not easy to reproduce on different units or in different patients; some women are physically unable to bend to the floor a prescribed number of times; some cannot climb steps or stairs. We have tried to develop an exercise programme which reproduces the sort of activities a woman may go through at home. That it does so was shown by Ali *et al.* (1983). It does not include running on the spot, which has been advocated by some, as this would be quite intolerable for the women in our series who are most wet (the 70-79-year-old group). However, it should include a series of coughs and this will be incorporated into our test programme at a later date.

In our experience, the activity which causes most urinary leakage in all types of patients is hand washing. Curiously, this is the most provocative exercise even in patients without bladder instability. Why this should be is unclear and deserves further study.

It is difficult to document reproducibility studies of this test; if a woman loses 1 ml on one occasion and 2 ml on the next there is 100% difference, yet the treatment of such a patient would probably not be affected. Similarly, if a woman loses 100 ml on one occasion and 200 ml on the next, the treatment is likely to be the same. If one attempts to "band" patients into mild, moderate and severe categories (say 0-10 ml, 10-100 ml, 100-1000 ml), there is a danger that a volume of 1 ml might put someone into a different treatment category. The banding of results is equally bad when used for follow-up studies. In an earlier study performed in our unit we used a logarithmic scale for comparing test results. In 50 women we repeated the test procedure after 3 to 4 days (Wood *et al.*, 1983). The total losses per hour during the two tests were compared. Sixty per cent of patients gave pad results which for practical purposes were the same (*i.e.* less than 2:1 difference). Clinical management would not have been affected in these cases. A further 16% showed a difference greater than 2:1 but less than 4:1. Of those who lost less than 10 ml on one occasion, 79% also lost less than 10 ml on the other occasion. Similarly, of those who lost more than 10 ml on one occasion, 78% also lost more than this on the other occasion. From these results we concluded that perineal pad testing is reproducible in the majority of cases.

It has been alleged that if patients void during the test they may leak less thereafter and be classified as continent when they are not. Our results suggest that voiding during the test period does not appear to make a great deal of difference to the overall test results. Furthermore, examination of the results in the patients who leaked less than 1 ml in the hour showed that voiding during the test had not influenced these results either. Thus we classified 24% of those who needed to void as continent, compared with 25% of those who did not void. This should dispel fears that voiding during the test gives rise to false negative results, *i.e.* a false diagnosis of continence.

In the wet patients (by our definition a leak of more than 1 ml during the activity period) we identified wetness after the first pad in 27% of cases, after the second pad in 43% and after the third pad in 68%. So, after the third pad (or after a shorter test) we would have missed a third of known incontinents. Furthermore, if we extrapolate from the curve (Fig. 11), it could be argued that a longer test (lasting more than 2 h from the time of the fluid intake) would pick up few extra patients. Also, this number would be kept low by the need to scale the results to the urine loss per hour (*i.e.* > 1 ml/h) and not to the total loss. By contrast, a test beginning soon after the fluid load might miss a considerable number.

Experience of this test so far is that it is extremely valuable in the assessment of the severity of urine loss in women complaining of incontinence. The exercise regimen appears to be the most important factor for making the test useful; voiding during the test does not influence the overall test result. Our plans for the future are to modify the test so that the more provocative exercises appear earlier in the test programme. This may enable us to shorten the test period. For the present test a full 1 h of activities starting about an hour after the intake of fluid appears to be necessary.

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The Authors

J. R. Sutherst, MD, FRCOG, Reader in Obstetrics and Gynaecology, University of Liverpool.

M. C. Brown, BSc(Eng), PhD, Principal Physicist, Institute of Medical and Dental Bioengineering, University of Liverpool.

D. H. Richmond, MRCOG, Lecturer in Obstetrics and Gynaecology, University of Liverpool.

Requests for reprints to: J. R. Sutherst, Department of Obstetrics and Gynaecology, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP.

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Hydrolytic Enzymes in Normal and Neoplastic Human Bladder Tissue

M. M. H. EL-SHARABASY and I. EL-DOSOKY

Urology and Nephrology Centre, Mansoura University, Mansoura, Egypt

Summary—The value of hydrolytic enzymes in 29 specimens of human bladder cancer has been assessed. Acid and alkaline phosphatases, γ-glutamyl transferase, arylsulphatases and lactate dehydrogenase were estimated in human bladder tumours and adjacent non-malignant tissue. Elevated enzyme levels were observed in the tumours rather than in the non-malignant tissue, except for adenocarcinoma. These increased levels were also noted in bilharzial bladder carcinoma but not in lymph node metastasis. Increased enzyme activity could be due to over-production by the tumour cells. It was concluded that the increase was associated primarily with the presence of tumours and the assay of these enzymes in biopsy specimens may have significant diagnostic and therapeutic implications.

Bladder carcinoma is the commonest malignant tumour in Egyptians (El-Sebai *et al.*, 1973) and so it is important to find tumour markers for the early detection of such tumours. The use of biochemical markers in screening for the presence of cancer and in the initial diagnosis of the disease has not received unqualified support. It has been established that some malignant cells produce substances which, when released into the circulation, reflect the presence and even the stage of the tumour (Waken, 1979). However, only a few of these indicators are useful in the primary diagnosis of common cancers (Lokich, 1978). Most of the well defined diagnostic biochemical and immunological tests are related to uncommon types of cancer. In some, enzymes have been used in the diagnosis of cancer and in the prognosis of the disease (Schwartz, 1973).

The aim of this study was to identify, characterise and quantify some hydrolytic enzymes in malignant and non-malignant tissues of the human bladder and to carry out comparative studies of these enzymes in bladder carcinoma in order to determine the alterations which may occur in malignant tissues. It was also hoped to improve the diagnosis of bladder carcinoma by analysis of biopsy tissue, if possible.

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Patients and Methods

The study group comprised 29 patients with bladder cancer (22 men and 7 women). The cystectomy specimens were received immediately after their removal. The anterior bladder wall (and/or posterior wall) was opened to show the malignant lesion. Macroscopically, the tumours were either polypoid fungating, ulcerative or infiltrative. Fresh wedge biopsies (0.2-1 g wet weight) were taken from the lesion and from the apparently normal bladder area and washed several times with cold saline and then homogenised in distilled water using an ice-cooled glass homogeniser. The homogenate was diluted to known volume and centrifuged for 10 min at 3500 rpm. The clear supernatants were removed and used directly for the enzyme assays.

The following enzymes were assayed in the supernatant of the homogenates of malignant and non-malignant bladder tissues.

The activity of acid phosphatase and alkaline phosphatase was estimated according to the method of Kind and King (1954) and King and Jegatheesan (1959) respectively, *i.e.* each supernatant was incubated in citrate buffer at pH 4.9 or in carbonate buffer at pH 10, using phenyl phosphate as a substrate, and the liberated phenol was measured photometrically by reduction with aminoantipyrine.

Table 1 Histopathological Variants of Bladder Cancer, Lymph Node Metastasis and Presence of Bilharzia

Type of cancer	*Grade* *I*	*II*	*III*	*Anaplastic*	*Lymph node*	*Bilharzia*
Squamous cell	6	8	1		5	12
Adenocarcinoma	4	2	1	3*	4	8
Transitional cell		1	1		1	1
Mixed	1†			1‡	1	2

* Signet cell carcinoma.
† Grade I squamous cell carcinoma and lymphocytic lymphoma.
‡ Anaplastic carcinoma and lymphoma.

The lactate dehydrogenase assay was performed kinetically at 37°C by the method of McQueen (1972).

Gamma-glutamyl transferase, catalysing γ-glutamyl group transfer between peptides and to L-amino acids, was assayed kinetically at 37°C by the method of Rosalki and Tarlow (1974).

Arylsulphatases, catalysing the hydrolysis of an aryl sulphate, were determined according to Rinderknecht *et al.* (1970), using p-nitrocatecholsulphate as the substrate.

Duplicate assays agreed, with a variation of less than 10%. Enzyme activity was related to 1 g wet weight of the bladder tissues.

The means, standard deviations and significance between the means were evaluated by the statistical methods of Snedecor (1956).

Results

Twenty-nine bladder cancers, both epithelial and non-epithelial malignant tumours, were included in the study (Table 1). Squamous cell carcinoma was the commonest tumour and lymph node secondaries were found in 33.3% of cases. Grade II was the commonest variant. Among the adenocarcinomas, Grade I was the commonest (40%), followed by signet cell carcinoma (30%). Secondaries in the lymph nodes occurred in 40% of the adenocarcinomas. A similar incidence of Bilharzia was found in all types of bladder cancer.

Table 1 demonstrates that low grade malignancy (grades I and II) was the commonest finding. Bilharzia ova were found in the urothelium in nearly all cases (79.31%) and lymph node metastasis was found in 37.93%.

Table 2 shows that the levels of alkaline phosphatase, arylsulphatases and lactate dehydrogenase in bladder cancer were significantly elevated ($P<0.01$) compared with those in non-malignant bladder tissues, while both acid phosphatase and γ-glutamyl transferase activity was almost significant ($P<0.05$).

On the other hand, the hydrolytic enzymes (acid and alkaline phosphatases, γ-glutamyl transferase and arylsulphatases) were increased in squamous cell carcinoma of the bladder but not in adenocarcinoma when compared with non-malignant tissues (Table 2). Enzyme activity in bilharzial bladder tumours was markedly increased when compared with activity in adjacent non-malignant tissue; with the exception of lactate dehydrogenase, however, the activity of these enzymes was not increased in the lymph nodes of bladder carcinoma.

Discussion

It is known that many lysosomal enzymes play an important role in the balance between health and disease (de Reuck and Cameron, 1963). Several reports have suggested that acid and alkaline phosphatases, lactate dehydrogenase, γ-glutamyl transferase and arylsulphatases are useful in the detection of different tumours (Dzialoszynski and Gniot-Szulzycka, 1967; Lokich, 1978; Beck *et al.*, 1979; Waken, 1979). Our results show that the clear-cut differences in these enzymes observed in non-malignant and malignant tissues of the bladder are very striking and may lead to potential diagnostic tests. Malignant tumours can be distinguished by the presence of elevated levels of these enzymes, except in the case of adenocarcinoma (Table 2).

The increased levels of these enzymes in bladder carcinoma may be due mainly to over-production by the tumour cells, as suggested by Lykourinas *et al.* (1982), and possibly also to other unknown factors involved in the regulation of their activity.

Our results in the bilharzia group could indicate that the bladder mucosa is affected mostly with bilharzial infection and the inflammatory process, and the elevation of these enzymes may be due to

Table 2 Means and Standard Deviations of the Activity (iu/g wet weight tissue) of Acid Phosphatase (Acid-ase), Alkaline Phosphatase (Alk-ase), Lactate Dehydrogenase (LDH), γ-Glutamyl Transferase (γ-GT) and Arylsulphatases (Ar-ase) in Malignant and Non-malignant Bladder Tissues

Type of cancer	*Acid-ase*	*Alk-ase*	*LDH*	*γ-GT*	*Ar-ase*
Total carcinoma					
Malignant tissues	0.0086 ± 0.0076	1.920 ± 1.630	10.88 ± 9.98	0.670 ± 0.58	0.025 ± 0.023
Non-malignant	0.0038 ± 0.0030	0.790 ± 0.610	4.50 ± 4.25	0.410 ± 0.38	0.011 ± 0.009
No.	(22)	(26)	(26)	(22)	(25)
P	<0.05	<0.01	<0.01	<0.05	<0.01
Squamous cell carcinoma					
Malignant tissues	0.0059 ± 0.0049	2.184 ± 1.645	11.21 ± 10.69	0.671 ± 0.50	0.026 ± 0.019
Non-malignant	0.0019 ± 0.0010	0.657 ± 0.406	4.27 ± 4.12	0.360 ± 0.32	0.010 ± 0.008
No.	(15)	(14)	(15)	(13)	(13)
P	<0.01	<0.01	<0.05	<0.05	<0.01
Adenocarcinoma					
Malignant tissues	0.0050 ± 0.0030	1.088 ± 0.850	6.47 ± 4.72	0.444 ± 0.26	0.028 ± 0.031
Non-malignant	0.0050 ± 0.0040	0.828 ± 0.721	3.88 ± 2.94	0.382 ± 0.35	0.017 ± 0.012
No.	(9)	(10)	(9)	(8)	(9)
P	NS	NS	<0.05	NS	NS
Bilharzia					
Malignant tissues	0.0060 ± 0.0034	1.900 ± 1.680	11.94 ± 10.76	0.585 ± 0.45	0.019 ± 0.010
Non-malignant	0.0039 ± 0.0025	0.704 ± 0.643	4.63 ± 4.61	0.226 ± 0.17	0.11 ± 0.009
No.	(22)	(22)	(21)	(18)	(20)
P	<0.05	<0.01	<0.01	<0.01	<0.01
Lymph node					
Malignant tissues	0.0057 ± 0.0050	1.724 ± 1.666	14.57 ± 12.36	0.949 ± 0.83	0.033 ± 0.030
Non-malignant	0.0036 ± 0.0030	0.842 ± 0.594	5.75 ± 4.72	0.425 ± 0.25	0.011 ± 0.007
No.	(11)	(11)	(11)	(8)	(12)
P	NS	NS	<0.05	NS	NS

NS = Not significant.

organ damage or bacterial infection associated with bilharzial infestation, together with other factors such as vitamin A deficiency (El-Aaser *et al.*, 1979).

On the other hand, it has been shown by Herz *et al.* (1973) that the basal levels of alkaline phosphatase activity in most cell lines derived from bladder carcinoma were extremely low, whereas acid phosphatase was within the range found in other human cells. It was also found that alkaline phosphatase was retained in cell lines established after chemical carcinogen treatment *in vitro*, in contrast to previous reports of the loss of this enzyme after treatment with bladder carcinogens *in vivo* in rats and mice (Wilson *et al.*, 1978). However, it is known that the bladder epithelium is rich in alkaline phosphatase (Martin, 1958), a difference which could be partly due to a difference in species and carcinogen. Moreover, bladder neoplasms vary in their histochemical characteristics and these variables may be correlated with variations in the clinical behaviour of such neoplasms.

Our biochemical findings are at variance with previous reports on the histochemical demonstration of lysosomal hydrolases in bladder carcinoma, but such discrepancies are not unusual. The detection of enzyme activity by histochemistry is influenced by several factors, including the type of tissue fixation, the solubility of the substrates or the end products, the length of incubation and the ability of the substrate to permeate a biological membrane (Lovett and Ryan, 1982).

The raised levels of alkaline phosphatase may be due to hyperosmolality, as a result of sialic acid elevation in bladder carcinoma (Herz and Koss, 1979) and some hormones, *e.g.* prednisolone, which initiate the synthesis of a modifier molecule that interacts with the enzyme to produce an alkaline phosphatase that has enhanced catalytic efficiency but is otherwise indistinguishable from the base-level enzyme (Herz *et al.*, 1974).

The significant increase in lactate dehydrogenase in bladder tumours in this study confirms the findings of Warren *et al.* (1962), that lactate dehydrogenase is exfoliated from the tumour to the surrounding fluids, urine, serum and cysts, which causes the increase of that enzyme in these fluids. This enzyme, like many other protein enzymes, may exhibit aberrant synthesis in cancer cells, where a mis-programming of genetic information leads to the aberrant synthesis of protein and results in isoenzymic alterations, and in tumour tissue there is a reactivation of genes that had been repressed during embryonic development (Macalalag and Prout, 1964; Bredin *et al.*, 1975).

The present study shows that γ-glutamyl transferase activity is significantly elevated in bladder carcinoma. Lum (1974) and Beck *et al.* (1979) have reported a similar increase in patients with hepatoma, and carcinoma of the pancreas and gall bladder.

Arylsulphatases constitute a group of enzymes found in all human tissues, with the exception of mature erythrocytes. The increase in their activity as reported in this study confirms the findings of Dzialoszynski *et al.* (1966), who reported increased arylsulphatase activity in several human carcinomas, including bladder carcinoma. Tumour cells undergo not only increased proliferation but also increased cell death; this destruction, combined with the release of their lysosomal enzymes, could contribute to the increased levels in urine (Morgan *et al.*, 1975).

We propose to undertake a prospective study on enzyme activity in patients with bladder carcinoma to see whether various forms of therapy affect the enzyme levels.

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The Authors

M. M. H. El-Sharabasy, PhD, Lecturer, Department of Chemistry, Mansoura University.

I. El-Dosoky, MD, Lecturer, Department of Pathology, Mansoura University.

Requests for reprints to: M. M. H. El-Sharabasy, Department of Chemistry, Mansoura University, Mansoura, Egypt.

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Origin of Carcinomas Causing Bladder Neck Obstruction Demonstrated by Immunoperoxidase Localisation of Specific Antigens

M. S. AL ADNANI

Department of Pathology, Kuwait University, Kuwait

Summary—The immunohistological demonstration of prostate specific acid phosphatase, prostate specific antigen, epithelial membrane antigen and keratin was used to ascertain the origin of five advanced carcinomas involving the bladder neck and causing obstruction. Five prostatic carcinomas, 10 transitional cell and 10 squamous cell carcinomas with schistosomiasis of the bladder were studied for comparison. The concomitant localisation of prostate specific antigen and keratin was most useful in ascertaining the origin of tumour invading the bladder in contrast to the multiple use of other epithelial markers. It showed that 2/5 were of prostatic origin and 3/5 were urothelial. The markers did not discriminate with certainty between invasive poorly differentiated transitional or squamous cell carcinomas.

Carcinomas invading the neck of the urinary bladder and causing obstruction are not uncommon and it can be difficult to reach a definite diagnosis based on conventional morphological grounds, especially in advanced cases when the specimens are small and fragmented. The two main primary sites of such neoplasms are the prostate or the bladder. While direct extensions from carcinoma of the colon or uterine cervix may involve the base and/or neck of the bladder, they are less difficult to diagnose clinically or histopathologically.

The immunohistochemical demonstration of prostate specific acid phosphatase (PSAP) and, more recently, prostate specific antigen (PSA) has been used successfully to determine the prostatic nature of tumours at their primary sites (Nadji *et al.*, 1980, 1981; Stein *et al.*, 1982) and, more important, in metastatic deposits (Jobsis *et al.*, 1978; Bentz *et al.*, 1982). Several epithelial markers have also been detected in the bladder epithelium as well as the prostate, such as carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA). Keratin, a cytoskeleton intermediate filament (Franke *et al.*, 1978), is often present in most normal and neoplastic epithelial tissues, especially in their basal and squamous cells (Schlegel *et al.*, 1980a, b), but is absent in the prostatic glandular epithelium and found only occasionally in the basal layer or the reserve cells of the prostatic ducts (Schlegel *et al.*, 1980a).

The localisation of PSAP and PSA prostate specific markers and EMA and keratin epithelial markers was used to ascertain the origin of neoplasms involving the bladder neck whose exact nature could not be ascertained by routine histological methods and comparing the distribution of these antigens in prostatic carcinomas, transitional carcinomas of the bladder and squamous carcinomas of the schistosomal bladder.

Materials and Methods

Formalin fixed, paraffin embedded transurethral biopsies were available from five advanced tumours which involved the bladder neck, caused obstruction and had a histopathological diagnosis of poorly differentiated carcinoma. Five prostatic carcinomas, 10 transitional carcinomas of the bladder and 10 squamous cell carcinomas of the bladder with schistosomiasis were used. In addition to

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Table Positivity Rate of Immunoperoxidase Stains for Prostate Specific Acid Phosphatase (PSAP), Prostate Specific Antigen (PSA), Epithelial Membrane Antigen (EMA) and Keratin in the Various Neoplasms Examined

Site and type	*PSAP*	*PSA*	*EMA*	*Keratin*
Prostatic carcinoma	5/5	5/5	5/5	0/5
Carcinoma involving the bladder neck	1/5	2/5	2/5*	3/5
Bladder: Transitional cell carcinoma	0/10	0/10	8/10	10/10
Squamous cell carcinoma with schistosomiasis	0/10	0/10	6/10	10/10

* The same tumours which were positive for PSA

the routine histological sections, which were stained with haematoxylin and eosin and periodic acid-schiff stains, 5-nm thick consecutive sections were cut and attached to chrome gelatin coated slides to be used for immunostaining.

An indirect immunoperoxidase procedure as described previously (Al Adnani *et al.*, 1974, 1975) and as modified for use on fixed, paraffin embedded sections (Burns, 1978; Al Adnani *et al.*, 1986) was employed. The primary antibodies used were polyclonal rabbit antihuman PSAP, PSA and keratin (molecular weight 56 and 69 k) diluted 10 times in 1:5 normal swine serum (NSS) and mouse monoclonal antibody to EMA used in a dilution of 1:20 in 1:5 NSS. The second layer was swine anti-rabbit immunoglobulin peroxidase labelled antibody in a dilution of 1:30 in 1:5 NSS. All of the specific antisera were obtained from Dakopatt A/S, Denmark. Positive and negative controls were included in each run of staining. The positive control for PSAP and PSA comprised sections from prostatic hyperplasia, sections of duct carcinoma of the breast for EMA, and for keratin sections from bladder mucosa adjacent to tumours or sections from ureters. The negative controls included the use of non-immune serum or sera absorbed with fresh homogenates of prostatic tissue or normal skin.

Results

The Table shows the positivity rate of staining for PSAP, PSA, EMA and keratin in the various tumours. All prostatic carcinomas were positive for both PSAP and PSA, while 1/5 of the tumours involving the bladder neck were positive for PSAP and 2/5 for PSA. The intensity of the PSA staining was more intense and uniform in contrast to the staining of PSAP in both prostatic hyperplasia and carcinomas (Figs 1 and 2). All bladder neoplasms and 3/5 of the tumours involving the bladder neck were negative for both PSAP and PSA. EMA was localised in all five prostatic carcinomas, 2/5 of the tumours involving the bladder neck and 8/10 and 6/10 of the bladder transitional and squamous cell carcinomas respectively. In the latter tumours the intensity was weaker and rather focal. The five prostatic carcinomas failed to show any positive staining for keratin. In contrast, keratin was demonstrated in all transitional and squamous carcinomas of the bladder and 3/5 of the neoplasms at the bladder neck (Figs 3 and 4). No striking difference in the distribution of keratin staining was observed in the transitional or squamous cell carcinomas, though a more intense staining reaction was seen in the well differentiated squamous cell carcinoma, especially in the keratin pearls (Fig. 3).

No staining was demonstrated in the negative controls for all of the markers.

Discussion

Immunohistological techniques have been used increasingly in the detection of functional or structural markers in normal and neoplastic tissues. The application of such procedures is most useful in invasive, poorly differentiated neoplasms, either to prove histogenesis at a primary site or to discover metastatic deposits, thus suggesting an occult primary. The result of the present study is yet another application of the immunoperoxidase method. It stresses the usefulness of the localisation of prostatic specific markers, PSAP and PSA and the epithelial marker, keratin, to determine the origin of advanced carcinomas involving the bladder neck where conventional histological methods failed to establish a definite diagnosis.

The results of the localisation of PSAP and PSA in the present study are in full agreement with several previous reports (Nadji *et al.*, 1980, 1981; Stein *et al.*, 1982; Heyderman *et al.*, 1984). The concomitant detection of other epithelial markers, such as CEA and EMA, with the prostate specific markers (Ellis *et al.*, 1984; Heyderman *et al.*, 1984) showed no advantage over the demonstrations of PSAP and/or PSA alone.

Reports of detection of epithelial markers in bladder carcinoma are also variable. For instance, the positivity rate for CEA ranged from 10 to 35% (Goldenberg *et al.*, 1976; Heyderman *et al.*, 1984), while the positivity rate for EMA reached 100% in

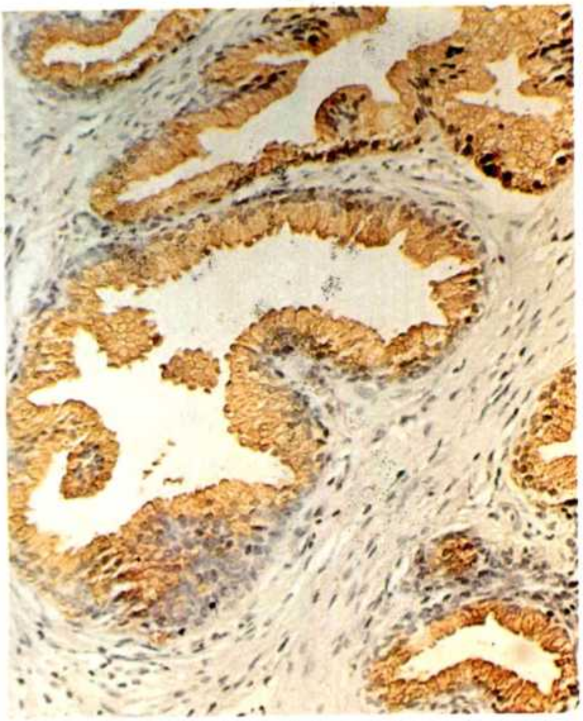

Fig. 1 Immunoperoxidase staining for PSA. Benign prostatic hyperplasia × 160.

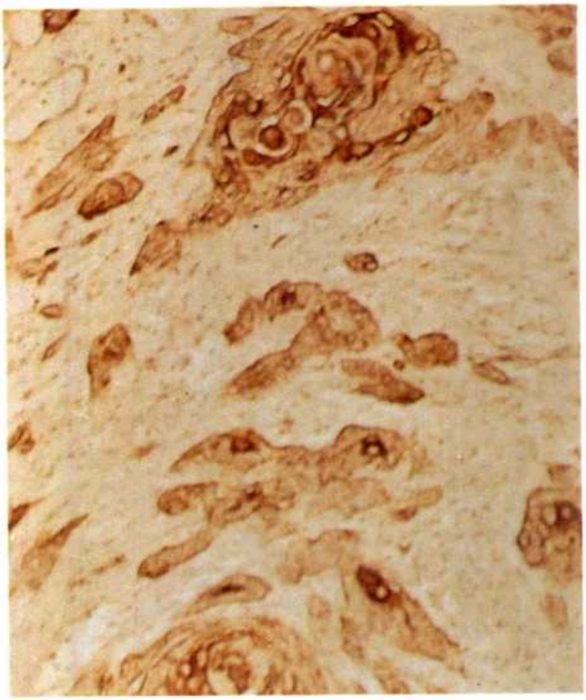

Fig. 3 Immunoperoxidase staining for keratin. Squamous cell carcinoma of the bladder × 160.

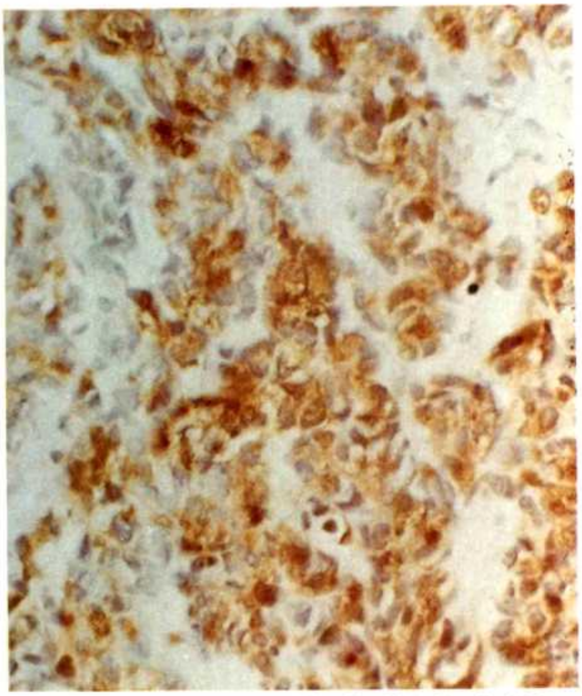

Fig. 2 Immunoperoxidase staining for PSA. Poorly differentiated carcinoma invading the bladder neck × 200.

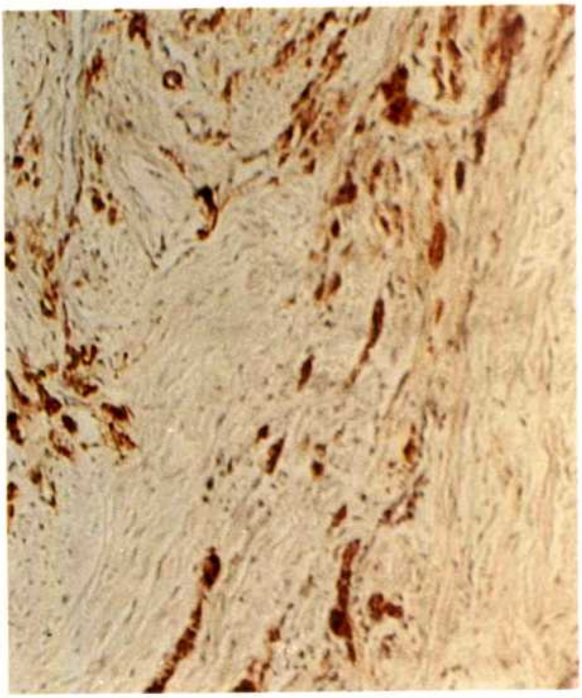

Fig. 4 Immunoperoxidase staining for keratin. Columns of invasive carcinoma of the bladder neck × 120.

transitional cell carcinomas (Heyderman *et al.*, 1984). In the current study, EMA was detected in 80% of transitional cell carcinomas and in 60% of squamous cell carcinomas, while keratin was 100% positive in carcinomas with and without schistosomiasis.

The variation in the positivity rate of the different epithelial markers at various sites could be due to several factors. The methods and rapidity of fixation, the nature and specificity of the antisera and the sensitivity of the immunohistochemical procedure employed are among the most important ones. This may explain the PSA positive, PSAP negative staining of one of the bladder neck carcinomas in our study (Nadji *et al.*, 1981).

In conclusion, the present study indicates that the concomitant demonstration of PSAP and/or PSA with keratin is most useful in ascertaining whether carcinomas involving the bladder neck are of prostatic or bladder origin. Such characterisation is very important in advanced cases, especially for palliative management, such as hormonal therapy in prostatic carcinomas versus radiotherapy or chemotherapy in advanced bladder cancer. No specific marker is able to discriminate between transitional and squamous cell carcinoma. This area invites further research, perhaps with the advancement in monoclonal antibody technology. Although the association between loss of ABH blood group isoantigens has been correlated with stage and grade of transitional cell carcinoma and its persistence in squamous cell carcinoma with schistosomiasis, it is not a definite marker of histogenesis. The author recently reported two cases of primary squamous cell carcinoma involving prostates severely affected by schistosomiasis by the demonstration of PSAP and/or PAP and keratin in the same tissues (Al Adnani, 1985). It is most likely that such tumours have arisen from reserve cells in the prostatic ducts which usually show keratin positivity (Schlegel *et al.*, 1980a) and express prostate specific markers.

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The Author

M. S. Al Adnani, PhD, MRCPath, FCAP, Associate Professor, Department of Pathology, Faculty of Medicine, University of Kuwait, PP. Box 24923, Safat, Kuwait.

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Treatment of Multiple Superficial Transitional Cell Carcinoma of the Bladder with Intravesical Yttrium-90

C. J. ALCOCK, K. R. DURRANT, J. C. SMITH and G. J. FELLOWS

Department of Radiotherapy and Oncology and Department of Urology, Churchill Hospital, Oxford

Summary—Thirty-eight patients with extensive multiple superficial transitional cell carcinoma of the bladder which could not be controlled endoscopically were treated with intravesical yttrium-90. Nineteen are alive at between 1 and 9 years. Short-term control of the disease was achieved in most patients. In those followed up for at least 3 years, 48% remained alive and well and 36% avoided cystectomy or other major treatment.

Malignant tumours of the bladder account for about 3% of all malignancies (International Union Against Cancer, 1979) and in the Western world 90% are of the transitional cell type. Most patients (approximately 80%) present with superficial (Ta or T1) tumours (Smith, 1983). The disease may be satisfactorily controlled in most cases by regular endoscopic procedures. Invasive disease may be expected to develop in 10 to 20% of these patients.

In some patients with multiple superficial tumours, the disease cannot be controlled by regular resection and/or cystodiathermy due either to rapid recurrence of disease or its widespread nature intravesically. In these patients, intravesical cytocoxics such as ethoglucid (Riddle, 1981) and thiotepa (Prout *et al.*, 1983) have been used. Other methods have included external irradiation (Poole Wilson, 1957) and radioactive suspensions (Ellis and Oliver, 1955). The use of intracavitary yttrium-90 in the treatment of superficial bladder tumours has been reported previously by Durrant and Laing (1975).

Patients and Methods

This study concerned 32 men and six women treated with intravesical yttrium-90 between January 1975 and February 1983. Their age range was 43 to 81 years (mean 66). All patients were diagnosed cystoscopically and histologically as stage T1 transitional cell carcinoma. The tumours were well or moderately differentiated, except for one case of poor differentiation. The interval from first diagnosis to treatment with intravesical yttrium varied between 8 months and 23 years (mean 5 years 1 month). Five patients had been cystoscoped on three occasions and 33 patients were cystoscoped on more than three occasions prior to yttrium therapy.

The indication for this treatment was either the discovery of multiple superficial bladder tumours too extensive to control by cystodiathermy or the recurrence of tumours at such a rate that they could not be controlled by endoscopic resection every 2 to 3 months. The patients were assessed by one of three urologists and by a single radiotherapist. Thirty-two patients received two yttrium instillations; one patient received three instillations and five patients one instillation.

Following treatment, patients were reviewed clinically and cystoscopically at 3-monthly intervals, decreasing to 6- or 12-monthly intervals according to the response.

Only one patient was lost to follow-up (due to his moving to another area) 4 years after yttrium treatment.

Technique

The technique used was similar to that described

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previously (Ellis and Oliver, 1955; Durrant and Laing, 1975).

Oliguria was induced by fluid restriction before the procedure. A Foley catheter was inserted and the bladder drained: 90 to 100 mCi of yttrium-90 obtained from Amersham International were marked with 1 ml of blue dye, diluted with 60 ml of gelatin at 37°C as stabilising agent in the isotope laboratory and transferred to the ward in a lead container. Using a sterile technique and a specially designed protected syringe, the yttrium was instilled into the bladder via the catheter. The patient's position was changed half-hourly to ensure that all bladder surfaces were covered by the liquid isotope. When the calculated treatment was completed at approximately 2 h, the bladder was drained into a special disposal container and washed out with irrigation solution. Using a mini-monitor scintillation counter, gamma radiation due to Bremsstrahlung was monitored at 10 cm, 1 metre and 2 metres to ensure complete drainage. After the standard decontamination procedure the patient was transferred to the gamma camera, to ensure that activity was less than 1 mCi yttrium-90.

Dosimetry was calculated according to the recommendations of Durrant and Laing (1975). A second treatment was given after an interval of 6 weeks to provide a total intended surface dose of 3000 cGy to the bladder mucosa. An isotope laboratory and decontamination facilities are mandatory for this treatment.

Complications of treatment

Early side effects were minimal. In only two patients were there any effects that could be attributed to the treatment. Two patients developed a contracted bladder at 1 year, which might also have been secondary to residual disease. Another patient developed haematuria a few months after treatment, thought to be due to treatment damage. No other early or late complications were documented by doctors involved in follow-up. In particular, no patient required cystectomy for radiation complications, but 14 patients required cystectomy for bladder cancer.

Results

The aims of treatment were to prevent death from tumour progression, to reduce the rate of recurrence of superficial bladder tumours to a level that could be managed by cystodiathermy, and to avoid cystectomy.

Recurrent tumour was noted cystoscopically within 6 months of yttrium instillation in 68% of cases. Recurrences were often small and could be managed by cystodiathermy.

Disease was controlled endoscopically in 17 of 38 patients (45%) and they have required no other form of treatment. Four of these patients have died, all from causes other than bladder cancer.

One patient has been lost to follow-up and disease was inadequately controlled in the remaining 20 patients. Cystectomy has been performed on 14 of these patients and recommended but declined in one further case. Of the five remaining patients, three have died from bladder cancer, one from other causes and one is now being considered for cystectomy.

In the group who underwent cystectomy because of failure of yttrium, eight have died from bladder cancer and six remain alive and disease-free.

Patients with minimum of three years' follow-up

Twenty-five patients were treated at least 3 years ago. Eleven remain alive, three having undergone cystectomy. The response of these patients to yttrium treatment is summarised in the Table. Another patient was alive at 4 years without further treatment but has since been lost to follow-up.

Thirteen patients have died. Four showed no response to yttrium, underwent cystectomy, but nevertheless died from bladder cancer. A similar fate attended two patients who had a transient response to yttrium. Four other patients had a transient improvement, one eventually dying from bladder cancer without further treatment and three dying from disease other than bladder cancer. Three patients showed a good response to yttrium but have died from disease other than bladder cancer (aged 78, 79 and 78 years).

Table Three-year Follow-up after Yttrium Instillation

	Survived 3 years	*Died of tumour*	*Died of other causes*	*Total*
No further treatment			1	1
One subsequent diathermy	1			1
Less frequent diathermy	7(1)†		2	10
Transient improvement		3	1 + 2*	6
No improvement	3	4		7
Total	11(1)†	7	4 + 2*	25

* Cause unknown
† Lost to follow-up after 4 years

The results show that there was improvement in 18/25 patients (72%) and this was prolonged in 12/24 (50%): 7/24 (29%) are known to have died from bladder cancer.

Discussion

We report a second series of patients treated with intravesical yttrium-90 in this department. The same indications for treatment were applied as in the previous series—namely extensive or rapidly recurrent disease no longer treatable by endoscopic resection. The alternative to intravesical yttrium was cystectomy, in a group of patients with an average age of 66, many of whom had medical contraindications to major surgery.

The incidence of severe toxicity or adverse effects was low, two patients developing haematuria that required transfusion and two complaining of frequency of micturition. This incidence compares favourably with that of intravesical cytotoxics, administration of which requires multiple catheterisations over a long period with a small risk of systemic lethal toxicity (Abbasian and Wallace, 1966) and a moderate incidence of chemical cystitis (Jacobi and Thüroft, 1981).

The results are slightly inferior to those reported in the earlier series, with 48% of patients with a minimum of 3 years' follow-up showing prolonged improvement: 36% survived and avoided major surgery. Toxicity was reduced in this series. Possible factors responsible for the difference between the two series include older age at treatment in the recent group (60 years versus 66 years) and improvements in endoscopic techniques, selecting more aggressive disease for referral.

Although intravesical yttrium-90 precludes the later use of external irradiation, it does not increase the morbidity or mortality rates of later salvage surgery, since only the superficial layers of the bladder are heavily irradiated.

Intravesical yttrium-90 is an effective and simple treatment for carefully selected cases of superficial bladder tumours, as an alternative to radical surgery. It helps to maintain a reasonable quality of life in elderly patients who would cope poorly with a cystectomy. It is especially effective in well differentiated tumours, none of the patients with this histological type dying from disease. In patients with moderately differentiated tumours not responding rapidly, early radical surgery is strongly advised.

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The Authors

C. J. Alcock, MRCP, FRCR, Consultant, Department of Radiotherapy and Oncology.
K. R. Durrant, MRCP, FRCR, Consultant, Department of Radiotherapy and Oncology.
J. C. Smith, MS, FRCS, Consultant Urological Surgeon.
G. J. Fellows, MS, FRCS, Consultant Urological Surgeon.

Requests for reprints to: J. C. Smith, Department of Urology, Churchill Hospital, Headington, Oxford OX3 7LJ.

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Identification of the Poor Risk Patient with "Prostatism" and Detrusor Failure

N. J. R. GEORGE, R. C. L. FENELEY and J. B. M. ROBERTS

Urodynamic Unit, Ham Green Hospital, Bristol

Summary—Twenty-five patients with "prostatism" and chronic retention of urine have been followed up for 4 years to determine the natural history of the disorder and results of elective treatment.

Twenty-one patients with low pressure during bladder filling maintained normal upper tracts and renal function; they were subdivided by micturition pressure into two groups which differed significantly in terms of both total bladder capacity and variance of capacity. Patients with good voiding pressures had a very satisfactory outcome following surgery, with almost complete relief of symptoms, but patients with poor voiding pressures obtained a poor symptomatic and urodynamic result from repeated surgical procedures. Four patients declined operation and the subsequent course of the disorder is described.

Four patients had painless retention associated with high pressure bladder filling, hydronephrosis and uraemia. Operation was successful in reversing these potentially terminal complications. None of the 25 patients developed acute retention.

Men with "prostatism" do not constitute a homogeneous population. Identification of specific patient groups enables an accurate prediction of the consequences of both conservative and operative management.

The finding of significant residual urine within the bladder of neurologically normal male patients following micturition raises important questions on their management and prognosis. Such patients with benign prostatic hypertrophy (BPH) and severe symptoms of outflow tract obstruction will generally be offered surgery, but it is not clear whether, or on what grounds, similar advice should be given to the large number of older men with milder symptoms who present to their practitioner more for reassurance than in expectation of an operation.

Digital examination of prostatic size is known to correlate poorly with the degree of obstruction (Turner-Warwick *et al.*, 1973). Both retrospective (Clarke, 1937) and prospective series (Birkhoff *et al.*, 1976; Ball *et al.*, 1981) have suggested that patients will not necessarily develop progressive lower tract symptoms or increasing urodynamic evidence of obstruction as time passes. Acute retention occurred in only 8 of 123 men with prostatic symptoms followed up by Craigen *et al.* (1969), though Birkhoff *et al.* (1976) reported a slightly greater incidence of complete blockage.

The risk of hydronephrotic change in patients with BPH remains difficult to determine. Upper tract dilatation was found in just 5% of 201 consecutive patients referred for urological opinion (Abrams *et al.*, 1976), but recent studies have suggested that such obstructive changes are limited to a particular subgroup described as having "high pressure chronic retention". Mitchell (1972) and George *et al.* (1983) considered that hydronephrosis occurs very rarely in "typical" bladder outflow tract obstruction. Lutzeyer *et al.* (1983), however, stated that the natural history of patients with BPH involves progressive stages of bladder wall hypertrophy leading finally to an atonic decompensation

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with hydronephrosis and obstructive renal failure, implying a need for operation in most cases.

We report our findings in a study designed to resolve these conflicting reports and to determine the result of both operative and conservative treatment of patients with "prostatism" (outflow tract obstruction) due to BPH.

Patients and Methods

The series constituted 25 male patients (age range 35-70 years, mean 56) referred by consultant urologists to the urodynamic unit with symptoms of outflow tract obstruction and who remained available for study over a 4-year period. All patients had residual urine greater than 100 ml after catheterisation but none had clinical evidence of neurological disease or prostatic cancer and midstream urine remained sterile and cell-free at every assessment.

All underwent intravenous urography and completed urinary frequency/volume charts as outpatients. On arrival a detailed history was recorded, a full examination performed and blood taken for estimation of haemoglobin, urea, electrolytes and creatinine levels. The method of urodynamic testing, involving initial flow studies, inflow and micturating cystometry, has been described in detail (George and Slade, 1979). In addition, baseline resting bladder pressures were recorded after the initial void but before drainage of residual urine, this measurement making a fundamental distinction between high and low pressure forms of retention. Patients with high pressure retention have abnormally raised intrinsic detrusor pressures throughout the filling phase (George *et al.*, 1983), whilst low pressure patients have normal baseline bladder pressures (equal to intra-abdominal pressure) during this part of the micturition cycle. The urodynamic report was passed to the consultants, who managed the patients according to their own judgement.

Repeat studies were performed 4 years later by the same investigator (NG), using the same method as in the original examinations, particular attention being directed toward obtaining an accurate account of any symptom changes that had occurred as a result of either operative or conservative treatment. Statistical analysis of urodynamic records was by the Kruskar-Wallis rank sum test for non-parametric data and standard tests for equality of variances. The terminology corresponds to that recommended by the International Continence Society.

Results

Painless Retention With Elevated Filling Pressure

Four patients exhibited raised intravesical pressure during the filling phase and presented with late onset enuresis in addition to minor symptoms of outflow tract obstruction which were limited to slight hesitancy and mild daytime frequency. A tense, palpable but painless bladder was detectable in each case. Urography demonstrated upper tract dilatation in all cases and serum creatinine was elevated in three, two of these patients being mildly hypertensive.

Three patients underwent transurethral resection. At the 4-year review, serum creatinine had returned to nearly normal and symptoms of enuresis and frequency had ceased, the patients pronouncing themselves satisfied with treatment. One patient aged 49 had refused operation, fearing retrograde ejaculation, and repeat urography demonstrated increasingly dilated and obstructed upper tracts associated with a rise of serum creatinine and a fall in creatinine clearance.

Painless Retention With Normal Filling Pressure

Twenty-one patients with low pressure recorded during the filling phase fell into two distinct groups according to intrinsic detrusor pressure exerted during the micturition phase. All had normal upper tracts on urography and blood urea, electrolytes and creatinine remained within normal limits throughout the study. One group was associated with a weak voiding pressure, the other with a more powerful or "appropriate" detrusor response to obstruction. Bladder capacity ($P<0.0075$) and variance of capacity ($F(9,10)=14.907$, $P<0.001$) were significantly different in the two groups (Fig. 1). No patient developed acute retention during the study.

High Pressure Voiders (Pdet 88-210 cm H_2O, mean 138) (Figs 2 and 3)

Eleven patients with a vigorous detrusor response to obstruction were older (mean age 61 years) than the weak detrusor group. Three patients considered their poor stream to have been present for more than 10 years; the remaining histories were of less than 3 years' duration and entirely typical of bladder outflow obstruction. Straining commonly hindered micturition but, if employed, tended to be used at the termination of the natural flow. No bladder enlargement was detected clinically prior to referral. Urodynamics demonstrated mild phasic instability in 4 of 10 patients with high pressure-

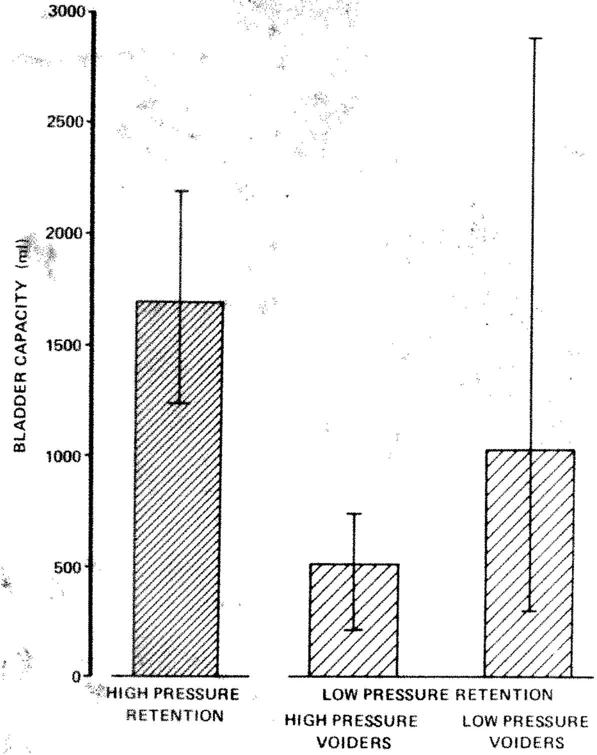

Fig. 1 Bladder capacity in low pressure chronic retention compared with data from 21 cases of high pressure chronic retention investigated by a similar technique. Variance of capacity $F(9; 10) = 14.907$, $P < 0.001$ was significantly different between the two low pressure groups.
Blocks-mean, Bars-range.

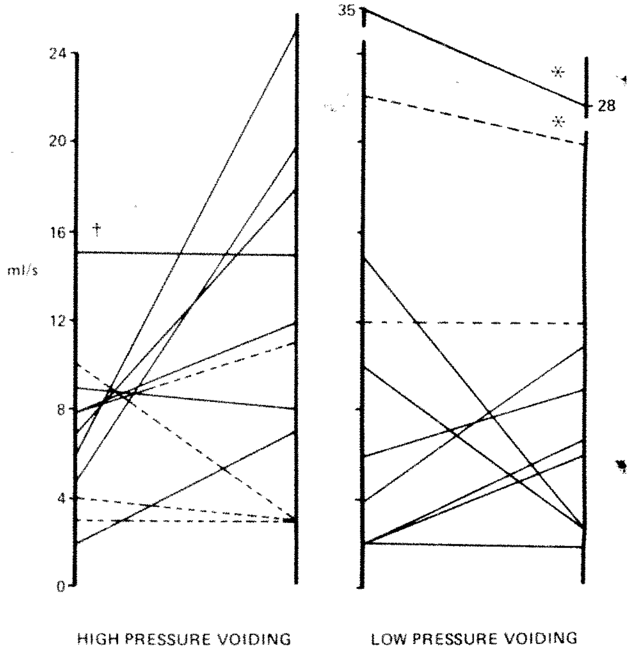

Fig. 2 Urine flow rates in low pressure chronic retention over a 4-year period. *Solid lines*: operated patients. *Broken lines*: non-operated patients. Patients with good quality detrusor muscles experience a satisfactory increase in flow rate post-operatively, whilst in only one non-operated case did the flow rate fall significantly. Flow rates in patients with poor quality detrusor contraction are very variable and respond unpredictably to operative treatment. *†: these patients had residual urines between 200 and 600 ml despite adequate flow rates.

low flow voiding. Retention in one patient was associated with marked urge and instability and Helmstein cystodistension was undertaken.

Six patients underwent transurethral resection on urodynamic advice, obtained relief of obstructive symptoms, and were discharged from further follow-up within 6 months. Mean flow rates pre- and post-operatively were 7.5 and 15 ml/s respectively. Four patients refused operation. In this subgroup cystometric capacity and residual urine did not uniformly increase and mean detrusor pressures at 4-year intervals were 144 and 152cm H_2O. Equivalent flow rates were 6.25 and 5 ml/s. At recall, all 11 patients, whether operated upon or not, felt that they were doing well and did not require any medical assistance.

Low Pressure Voiders (Pdet 8-68 cm H_2O, mean 28) (Figs 2 and 3)

The 10 patients with a weak voiding pressure were by no means all elderly (mean age 51 years) and complained of persistent symptoms, the mean duration in those with objective case records being 9½ years. Daytime frequency, suprapubic discomfort, marked hesitancy and straining throughout the effort to void were the most common complaints. Only one patient had nocturia more than once per night. Abdominal examination revealed an enlarged bladder by percussion rather than palpation in five patients. All patients had stable inflow tests often to large capacity (Figs 1 and 4) but subtracted detrusor pressure was weak and ineffective in emptying the bladder. Only two patients could further aid emptying with the Valsalva manoeuvre.

In an attempt to cure symptoms, 10 transurethral resections and five vesicoplications were performed on eight patients, one patient undergoing two plication operations. Two patients received no operation. Four years later, intrinsic pressure and flow rate were either unchanged or slightly worse, and only four patients considered themselves improved though not normal, whilst six felt that they were no better and were continuing to attend outpatient clinics on a regular basis.

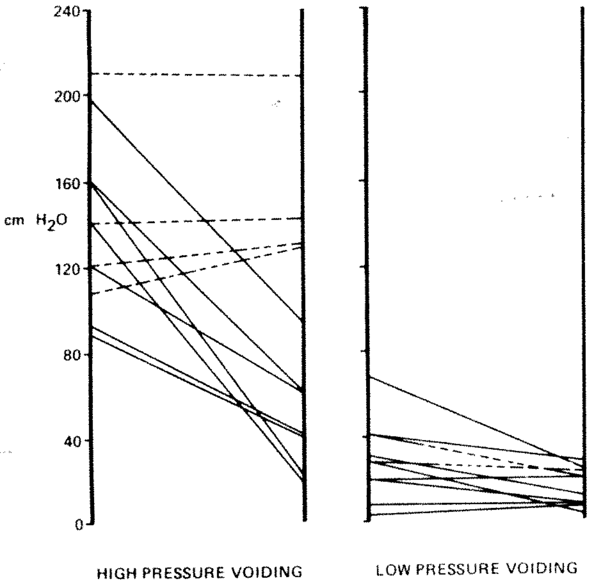

Fig. 3 Detrusor pressure at maximum flow (equivalent to Figure 2) in low pressure chronic retention over a 4-year period. Solid lines: operated patients. Broken lines: non-operated patients. Pressure characteristically drops after operation in patients with good quality detrusor muscles but remained vigorous in four patients refusing operation, showing no sign of decompensation despite very high initial values. Pressure developed by underactive muscle continues to diminish whether or not operation is performed.

Discussion

An essential prerequisite to the study was to choose a sensitive physiological definition of chronic retention so as to detect the earliest changes of bladder decompensation which, in time, may lead to the gross clinical forms of retention described by other authorities (Mitchell, 1972). It was considered that, following a normal (not over-full) micturition, a residual urine of approximately 25% or greater of the normal adult physiological bladder capacity constituted a significant inability to empty the bladder. Thus all patients with "prostatism" who were found on catheterisation to have residual urines of 100 to 120 ml or greater were included in the prospective study.

The cases of high pressure retention conformed exactly to the clinical pattern fully described elsewhere (George *et al.*, 1983). It is notable that neither acute painful retention nor atonic decompensation occurred in the patient who declined operation and in whom all observations pointed towards progressive obstructive renal failure.

All patients with low filling pressure had normal upper tracts. It would seem reasonable to propose that—in contrast to the high pressure group (Holden *et al.*, 1984)—ureteric peristalsis was able to effect urine transfer into the bladder without difficulty despite the presence of phasic unstable waves in some patients. A clear and significant distinction emerged between the presentation, urodynamic observations and response to treatment in the two voiding subgroups.

The case histories of prostatic patients with high pressure voiding were generally clear cut, the urodynamic findings unequivocal and results of surgery very satisfactory. The four patients who refused operation allowed a unique opportunity to observe the reaction of the detrusor muscle to severe long-term obstruction; despite the small numbers there are few, if any, reports in the literature of conservative treatment under such conditions. After 4 years, micturition pressure had not fallen, whilst bladder capacity and residual urine showed little consistent change. These findings underscore previous observations that prostatic patients do not necessarily deteriorate as time passes (Clarke, 1937; Craigen *et al.*, 1969). Ball *et al.* (1981) also found little urodynamic change in 17 obstructed patients over a 5-year period.

It would appear that long held views regarding bladder "overstretching", "decompensation" and the likelihood of acute retention in patients with "good quality" detrusor muscles require careful reconsideration. This does not, of course, exclude the possibility that a sudden stress (for example, overdelayed micturition due to a long car journey) might not upset the balance of forces. However, the observation that these patients have good quality detrusor muscles should be a source of confidence for the practitioner who advises his patient along conservative lines; such advice will not be prejudicial to a satisfactory outcome from surgery should this eventually become necessary.

The patients with weak and underactive detrusor muscles, by contrast, tended to be younger, had a long duration of symptoms, and responded poorly to numerous operative procedures. Though no patient developed acute retention, severel mentioned "near misses" with prolonged hesitancy, suprapubic discomfort and dribble-stream. Transurethral resection and vesicoplication (Roberts *et al.*, 1979) appeared to offer some symptomatic relief, though often the urodynamic effect was only a temporary arrest of the distension process. Nevertheless, the removal of any obstruction is probably very important in these patients with poor detrusor reserve, since the bladder must be given every chance to avoid being overstretched. Thus, para-

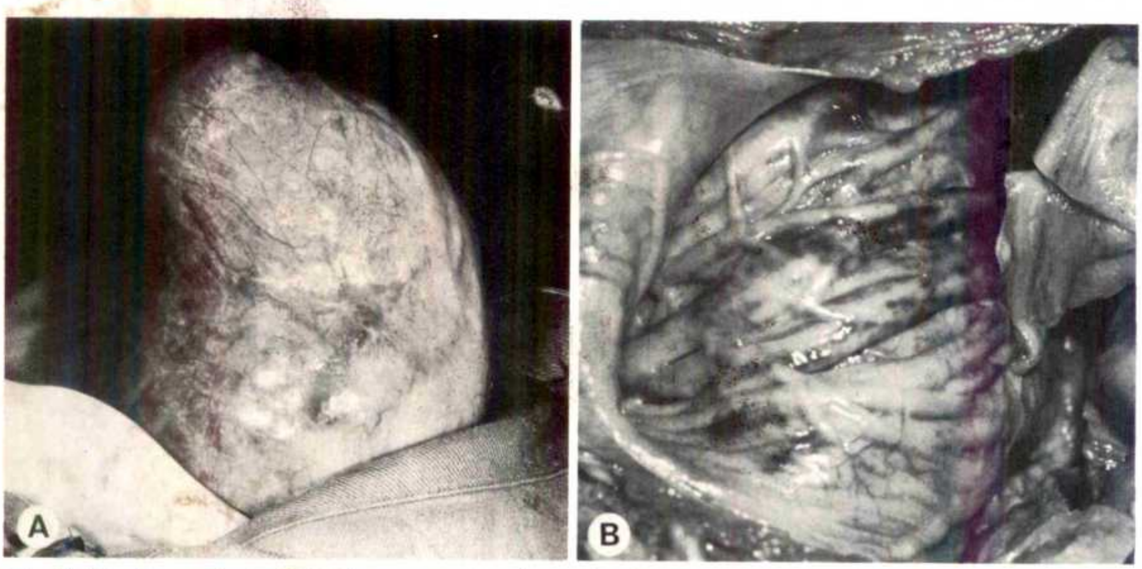

Fig. 4 Bladders from patients with (A) low pressure chronic retention (low pressure voiding) and (B) high pressure chronic retention. Note gross trabeculation and thick wall compared with almost translucent low pressure bladder. It is difficult to imagine that these two bladders are part of the same disorder process.

Table Clinical and Prognostic Factors in Patients with Prostatism and Residual Urine

				Chronic retention of urine Classification and characteristics				*Prognosis*		
	Filling phase pressure	*Voiding phase pressure*	*Flow*	*"Prostatic" symptoms*	*Length of history*	*Upper tracts*	*Serum creatinine*	*Acute retention*	*Non-operated*	*Operated*
HPCR	High	High	Low	Often absent	? lifelong	Usually dilated	Commonly raised	Rare if ever	Death uraemia	Probably good
LPCR	Low	High	Low	Classical of BOO	Often short (<3 yrs)	Normal	Normal	Unusual	? Compensate for obstruction	Good
		Low	Low	Often atypical Valsalva	Often long (>5 yrs)	Normal	Normal	Probably common	Severe detrusor decompensation	Poor

HPCR = high pressure chronic retention.
LPCR = low pressure chronic retention.
BOO = bladder outlet obstruction.

doxically, it is not the obstructed but the underactive patients who most require referral for surgical opinion—conservative treatment is inadvisable in this group.

In summary, the evidence suggests that it is very unlikely that the weak voiders are the end result of powerful voiders who have declined operation; in particular, such an hypothesis would require that the former would generally be older than the latter—the reverse, however, is the case. Symptoms, length of history, voiding pressures, bladder capacity and variance of capacity were significantly different in the two groups. The inequality of variance confirmed that whilst high pressure voiders tended to maintain low volume, "compact" bladders, poor voiders were inclined to develop increasingly distended bladders over a period of time.

In the light of these findings the aetiology of the weak detrusor group remains obscure. Webster *et al.* (1980) proposed that the low pressure-low flow voiding seen in younger men with chronic prostatitis or prostatodynia (Osborn *et al.*, 1981) may predispose to the large atonic bladder observed in older men and the group may be similar to the "idiopathic detrusor failure" patients studied by Kirby *et al.* (1983). It is also pertinent to note that acute painful retention was considered by Powell *et al.* (1980) to be most likely to occur in patients with severe hesitancy, decompensated bladders and large residual urines—an almost exact description of the weak voiding group.

This prospective study has identified three discrete patient groups which seem most unlikely to be progressive stages in a common response to outflow obstruction. A summary of the observations as related to prognosis (Table) may help to identify problem patients with "prostatism" and thus obtain the best possible results from transurethral surgery.

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The Authors

N. J. R. George, FRCS, formerly Research Registrar, Ham Green Hospital. Now Senior Registrar/Lecturer, Department of Urology, University Hospital of South Manchester, Manchester.

R. C. L. Feneley, FRCS, Consultant Urological Surgeon, Ham Green Hospital.

J. B. M. Roberts, ChM, FRCS, Consultant Urological Surgeon, Royal Infirmary, Bristol.

Requests for reprints to: N. J. R. George, Department of Urology, University Hospital of South Manchester, Nell Lane, Withington, Manchester M20 8LR.

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A High Risk Factor Score in the Management of Benign Prostatic Hyperplasia

N. P. GUPTA, N. K. MOHANTY, P. S. REDDY, S. N. WADHWA and SARINDER MAN SINGH

Department of Urology, All-India Institute of Medical Sciences, New Delhi, India

Summary—To evaluate high risk factors in the management of benign prostatic hyperplasia, a scoring system has been devised which includes associated medical diseases and such complications as retention, infection and uraemia. A score of 1 to 3 was given for each high risk factor. Patients with a total score of 1 to 3 were regarded as grade I, 4 to 6 as grade II and more than 7 as grade III. Three hundred and fifty cases of benign prostatic hyperplasia were evaluated and the patients' hospital stay, complications and mortality compared.

Benign prostatic hyperplasia (BPH) is a disease which occurs after the age of 40 years, when men tend to suffer from many other associated medical diseases such as hypertension, myocardial infarction, heart block, coronary artery disease, diabetes mellitus, chronic airway obstructive disease, cerebrovascular accidents, malignancies, tuberculosis, anaemia with bleeding disorders and various age-associated factors (Singh *et al.*, 1973; Chilton *et al.*, 1978). Complications such as retention, infection and uraemia also increase the risk of prostatectomy (Blandy, 1981).

To evaluate the high risk factors in BPH we evolved a scoring pattern which included associated medical diseases and complications. A score of 1 to 3 was given for any associated high risk factor. Patients scoring 1 to 3 were graded as grade I, 4 to 6 as grade II and more than 7 as grade III. Patients with no score were not considered.

Patients and Methods

We reviewed 350 patients with BPH treated at this Institute between 1981 and June 1984. High risk factors were correlated with post-operative complications, duration of hospital stay, type of anaesthesia, amount of blood transfused, mortality, etc.

All patients underwent a detailed clinical examination and pre-operative assessment. Pulmonary function tests and isotope renal scans were also done if indicated. Any complicating medical diseases were assessed by the physicians and treatment instituted.

Patients whose prostatic weight was less than 60 g were treated by transurethral resection (TURP) and those whose prostatic weight exceeded 60 g were managed by transvesical or retropubic approaches, depending on the surgeon's preference. No perineal prostatectomy was performed in this series. Distilled water was used as irrigating fluid during transurethral resection and prophylactic antibiotics were used in all cases.

Results

Of the 350 patients, 117 (33%) were grade I, 175 (50%) were grade II and 58 (16%) were grade III. The youngest patient was aged 40 years and the oldest 93; 68% had a history of either acute or chronic retention of urine with periods of indwelling catheterisation ranging from 2 weeks to 1 year before surgery. Sixty-eight patients (19%) had cardiovascular diseases (myocardial infarction, angina, ischaemic heart disease, heart block with pacemaker and sick sinus syndrome) and 65 patients (18%) had chronic obstructive airway dis-

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Table 1 Risk Factors and Scores

	Scores		
Risk factors	1	2	3
Age (years)	60-70	71-80	81
Retention of urine/indwelling catheterisation	Yes	—	—
Urinary tract infection	Yes	—	—
Anaemia	11-12 g%	8-10 g%	≤8 g%
Previous malignancy	Yes	—	—
Renal failure (Bl. urea >70 mg%) (S. creatinine >2 mg%)	Reversible	—	Irreversible
Cerebrovascular accidents	6 months	3-6 months	Less than 3 months
Diabetes mellitus	Mild, controlled without drugs	Moderate, controlled with drugs	Uncontrolled
Hypertension	Mild, 150/90 mmHg	Moderate, 200/120 mmHg	Severe, 280/150 mmHg
Heart block	Incomplete	—	With pacemaker
Myocardial infarction, angina pectoris	6 months	3-6 months	Less than 3 months
Chronic airway obstructive disease	Dyspnoea on unusual exertion	Dyspnoea on moderate exertion	Dyspnoea at rest

ease (chronic bronchitis, bronchial asthma, pulmonary tuberculosis, pleural effusion and pneumonitis). Twenty-two patients (6%) had a history of previous malignancy: 14 (4%) had bladder tumours and eight patients (2%) had other malignancies such a renal carcinoma (3), rectal carcinoma with abdomino-perineal resection (2), squamous cell carcinoma of the anal canal (1), lymphatic leukemia (1), and one patient had pulmonary metastasis with an unknown primary (Table 1, 2).

Two hundred and ninety-eight patients (85%) underwent transurethral resection—39 (11%) transvesical and 13 (3%) retropubic prostatectomies (Table 3). The weight of prostate gland removed was less than 30 g in 250 cases (71%), 31 to 60 g in 67 cases (19%), 61 to 120 g in 32 cases (9%) and more than 120 g in one case (0.29%) (Table 4). Two hundred and ninety-seven patients (85%) had spinal anaesthesia, 50 (14%) general and three (0.85%) epidural anaesthesia (Table 5). One hundred and twenty-two patients (41%) who underwent transurethral resection required blood transfusion and all of those who underwent open prostatectomy (52 patients) required blood.

Twenty-seven patients (9%) who underwent transurethral resection were discharged within 5

Table 2 Incidence of High Risk Factors

Factors	*Grade I*	*Grade II*	*Grade III*	*Total*	%
Age (years)					
60-70	55	92	25	172	49.1
71-80	12	53	20	85	24.3
>81	0	4	11	15	4.3
Anaemia (>12 g%)	38	128	54	220	62.86
Hypertension (>150/90 mmHg)	24	46	32	102	29.14
Cardio-vascular disease	8	41	19	68	19.43
Chronic obstructive airway disease	12	33	20	65	18.57
Diabetes mellitus	5	16	12	33	9.43
Urinary tract infection	29	106	47	182	52.0
Renal failure	2	14	28	44	12.5
Carcinoma prostate	5	14	3	22	6.29
Cerebrovascular accident	0	5	3	8	2.3
Retention of urine with catheterisation	58	132	47	237	67.7

Table 3 Types of Prostatectomy

Type	*Grade I*	*Grade II*	*Grade III*	*Total*	%
Transurethral	92	152	54	298	85.14
Transvesical	20	17	2	39	11.3
Retropubic	5	6	2	13	3.7

Table 4 Weight of Prostate Gland Removed

Weight (g)	*Grade I*	*Grade II*	*Grade III*	*Total*	%
30	81	127	42	250	71.4
31-60	25	30	112	67	19.1
61-120	10	18	4	32	9.1
120	1	0	0	1	0.29

Table 5 Type of Anaesthesia

Type	*Grade I*	*Grade II*	*Grade III*	*Total*	%
Spinal	95	150	52	297	85
General	21	24	5	50	14.3
Epidural	1	1	1	3	0.85

Table 6 Post-operative Hospital Stay

No. of days	*TURP* *Grade I*	*Grade II*	*Grade III*	*Total (%)*	*%*	*Open* *Grade I*	*Grade II*	*Grade III*	*Total (%)*	*%*
5	10	14	3	27	9.06	0	0	0	0	0
6-10	60	100	38	198	66.4	2	2	0	4	7.7
11	22	38	13	73	24.5	23	21	4	48	92.3

Table 7 Complication Rate

Grade	*TURP (%)*	*Open (%)*
Grade I	15/92 (1.63)	5/25 (20)
Grade II	20/152 (1.30)	12/23 (52.17)
Grade III	6/54 (1.10)	3/4 (75.00)
Total	41/298 (13.75)	20/52 (38.46)

Table 8 Complications

Complications	*Grade I*	*Grade II*	*Grade III*	*TURP*	*Open*
Haemorrhage	7	11	2	16	4
Meatal stenosis	4	1	0	3	2
Wound infection	2	2	1	0	5
Stress incontinence	2	4	0	4	2
Epididymo-orchitis	1	2	1	2	2
Residual adenoma	2	4	0	6	0
Bladder perforation	1	0	1	2	0
TURP syndrome	0	1	1	2	2
Urinary tract infection (post-operative)	5	2	18	18	7

Table 9 Mortality Rate

Types of prostatectomy	*Grade I*	*Grade II*	*Grade III*	*Total*	*%*
TURP	0	1	2	3/298	1.0
Open	0	2	0	2/52	3.8
Total	0	3	2	5/350	1.43

days and 198 (66%) within 10 days compared with only four (7%) treated by open surgery. The post-operative stay was shorter in grade I and grade II patients than in grade III cases (Table 6). There were post-operative complications in 41 patients (13%) who underwent transurethral resection and in 20 (38%) treated by open surgery (Tables 7 and 8).

Three patients died after transurethral resection and two after open surgery. There were no deaths in grade I patients (Table 9).

Discussion

Various workers have tried to correlate the effects of associated medical disease with the morbidity and mortality rates following prostatic surgery (Singh *et al.*, 1973; Blandy, 1981). We have modified the grading system by excluding patients with no high risk factors and including those with complications such as infection, retention, uraemia and malignant disease.

The high risk factor scoring and grading system which we have described does not measure accurately but does give some idea of the type of case we are dealing with and the risk involved. By instituting appropriate measures we have achieved low mortality and morbidity rates even in poor risk patients who would otherwise be relegated to life with permanent suprapubic or urethral catheters.

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The Authors

N. P. Gupta, MS, MCh(Urol), Assistant Professor.
N. K. Mohanty, MS, Senior Resident.
P. S. Reddy, MS, MCh(Urol), Senior Resident.
Sarinder Man Singh, FRCS, FAMS, Professor.

Requests for reprints to: N. P. Gupta, Department of Urology, All-India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

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Post-hysterectomy Urethral Dysfunction: Evaluation and Management

S. A. FARGHALY, J. R. HINDMARSH and P. H. L. WORTH

Institute of Urology, London

Summary—A retrospective study of the functional alteration of the urethra following hysterectomy was made in 98 patients. Three groups were identified. Sixty per cent (group A) had stable stress urinary incontinence, 27.8% (group B) had high pressure detrusor instability and 12.2% (group C) had voiding dysfunction. Some of the patients in group A were treated medically and others surgically. Those in group B were treated with oxybutinin and those in group C were treated surgically. The cure rate in group A ranged from 55 to 89%; in group B it was 82% and in group C between 90 and 100%.

Total hysterectomy may cause debilitating urinary symptoms. Many women who attend urological clinics with this problem date the onset of their symptoms from this operation (Hamley, 1969). Many hysterectomies are performed in pre-menopausal women and the incidence of micturition symptoms in women of this age group without concomitant gynaecological disease or gynaecological surgery is very high. Among the causes of disorders of the lower urinary tract are injuries to the pelvic nerves, post-operative bladder changes, accidental lesions caused by inadequate post-operative bladder drainage and urinary tract infection. This retrospective study was undertaken to assess the post-operative incidence of micturition symptoms and also to evaluate management.

Patients and Methods

Ninety-eight female patients with post-hysterectomy bladder dysfunction were studied. They complained of lower urinary symptoms and showed no neurological abnormalities. All patients were investigated by flow studies and voiding cine-urethrocystography with simultaneous pressure recordings. Repeated urine analyses and cultures were performed before and after the study. The investigation was carried out on an out-patient basis.

If the patient had not emptied her bladder for about 2 h before the investigation, she was seated on the commode and asked to void naturally. The urine was received in a collecting bowl and run into a measuring cylinder. A pressure recording catheter with its tip placed at the bottom of the measuring cylinder recorded on one channel of a three-channel direct writing recorder via a transducer. The changes in pressure were proportional to the flow and were calibrated in ml/s. If the patient had arrived with an empty bladder she was catheterised with full aseptic precautions and the bladder was filled with sterile distilled water. The catheter was then removed before seating the patient on the commode and the flow study was carried out as described. The patient was returned to the couch and catheterised using a soft rubber 18 F catheter. On this occasion the bladder was filled with a 50% solution of sterile barium sulphate suspension (Micropaque) until the patient indicated an urge to void, when the bladder capacity was recorded. A fine pressure recording catheter (2 mm external diameter) was inserted into the bladder and strapped to the patient's thigh. The intravesical catheter via a separate transducer recorded changes in intravesical pressure on a separate channel of the

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Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

recorder. The patient was then positioned with a 23-cm image intensifier on her right and an X-ray tube on her left and a preliminary X-ray was made to confirm proper alignment. Once the alignment had been verified and a film of the bladder at rest obtained, the patient was asked to cough and relax and then strain and relax while films were exposed and pressures recorded. She was then asked to void. As soon as it was noted that voiding had commenced, filming and pressure recording were continued and the patient was asked to stop voiding in mid-stream. No further X-rays were taken until voiding was completed, when a final film revealed the amount of residual contrast medium in the bladder. No bladder washout was required but increased fluid intake over 12 h was advised.

Sixty patients had urethral pressure studies. A combination of microtip transducers linked to a Sirius I with a 10 MByte Winchester microprocessor system, complete with a purpose-built interface and software, was used so that synchronous studies could be performed. A 9 F five-sensor silicon rubber catheter was used. Rectal pressure was determined by a standard fluid-filled catheter and external transducer. All pressure sensors were calibrated against a water column.

Results

The distribution of patients according to age showed that 13 (13.3%) were aged 31 to 40 years, 37 (38.8%) were between 41 and 50 years, and 48 (48.9%) were aged 51 to 67 years. On reviewing the operative procedures it was shown that of the 64 patients who underwent abdominal hysterectomy, 17 had both ovaries removed. Thirty-four patients had a vaginal hysterectomy, usually associated with anterior colporrhaphy (Table 1).

Three groups were identified. Sixty per cent (group A) had stable stress incontinence, 27.8% (group B) had high pressure detrusor instability and 12.2% (group C) had voiding dysfunction (Table 2). Of the 60 patients with stress urinary incontinence, nine had a mild degree of incontinence and were treated with pelvic floor exercises. Twelve had a moderate degree of incontinence and were treated with alpha-adrenergic stimulants. Five patients with an incompetent bladder neck were treated with Teflon injection and 19 with an incompetent bladder neck associated with anterior vaginal wall prolapse were treated with colposuspension. Fifteen patients had an incompetent bladder neck and were treated with a Marlex sling (Table 3). Twenty-seven patients with high pressure detrusor instability were treated with oxybutinin chloride; 82% were cured and 18% failed to respond (Fig. 1). Of the 11 patients with voiding dysfunction, 10 were treated with urethral dilatation and one (with bladder neck dyssynergia) underwent bladder neck incision (Fig. 2).

Table 1 Hysterectomy Producing Urinary Symptoms

Operation	*No. of cases*	*%*
T.A. hysterectomy and BSO	17	17.3
T.A. hysterectomy with conservation of one or both ovaries	47	48
Vaginal hysterectomy	34	34.7

Table 3 Methods of Treatment and Outcome in Patients with Stable Stress Incontinence With or Without Low Pressure Detrusor Instability (15cm H_2O)

	No. of patients	*Number cured*	*% cured*
Pelvic floor excercises	9	6	65
α-Adrenergic stimulant	12	9	79
Teflon injection	5	3	55
Colposuspension	19	17	89
Marlex sling	15	13	84

Table 2 Results in Three Groups of Patients

	No. of patients	*%*	*Diagnosis*
Group A	60	60	Stable stress incontinence
Group B	27	27.8	High pressure detrusor instability
Group C	11	12.2	Voiding dysfunction

Discussion

Flow studies combined with cine-urethrocystography and pressure recordings help to pinpoint the underlying cause of incontinence and lead to effective treatment. Similar methods of investigation include flow studies (Smith, 1968), simple radiographic studies (Jeffcoate and Roberts, 1952), cine-fluorographic studies (Lund *et al.*, 1957; Haydon *et al.*, 1963; Turner-Warwick and Whiteside, 1970) and combined flow and cine-fluorographic

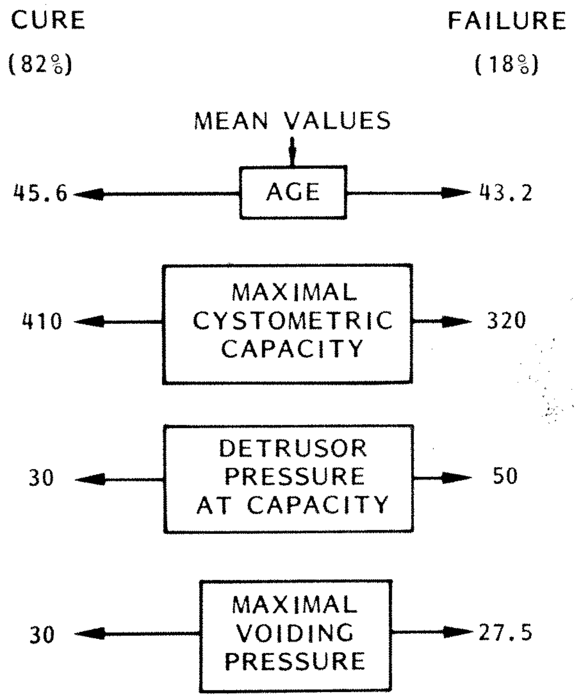

Fig. 1 Patients with high pressure instability (< 15cm H_2O) treated with oxybutinin.

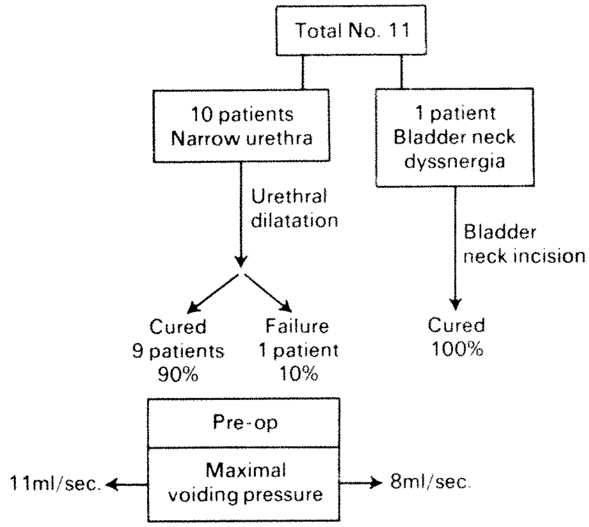

Fig. 2 Results of treatment in patients with voiding dysfunction.

studies (Tanagho and Donald, 1966; Bates and Corney, 1971). With recent advances in urodynamics (Brown and Wickham, 1969), measurement of the intraurethral pressure has become a useful diagnostic tool (Edward and Malvern, 1974; Asmussen, 1976).

The importance of pelvic floor exercises to re-establish tone and function, especially after childbirth, is well known, since the voluntary muscles of the pelvic floor contribute about one-third of the value of total urethral closure pressure (Einhorning, 1961). The correct exercising of these muscles has always presented problems, though medical stimulation of the alpha-adrenergic receptors of the urethra is reported to be of value (Diokno and Taub, 1975; Obrink and Bunne, 1978). Periurethral Teflon injection has been reported to be effective in restoring urinary continence (Berg, 1973; Politano *et al.*, 1974; Lim *et al.*, 1983) and in this study the failure rate was 45%. The cure rate for stress incontinence following anterior colporrhaphy ranges from 48 to 60% (Jeffcoate, 1965; Low, 1967; Ross and Shingleton, 1969) and the results reported for retropubic operations have been considerably better (Terzian, 1965; Burch, 1968). Oxybutinin reduces urgency, urge incontinence and frequency, and symptomatic improvement ranging from 69 to 75% has been reported by Diokno and Lapides (1972) and Moisey *et al.* (1980). Dyssynergic bladder neck occlusion is a rare cause of female bladder outflow obstruction and is commoner in diabetics and patients with very low detrusor activity.

Anterior incision avoids the risk of fistula formation in the vaginal wall, which may follow posterior or postero-lateral incision, and allows retropubic re-closure in the event of troublesome incontinence (Turner-Warwick, 1973). Urethral narrowing can be relieved by dilating the urethra to at least 45 F (Davis, 1956).

It is concluded that urodynamic evaluation of incontinence after hysterectomy can be extremely useful in the management of this condition.

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The Authors

S. A. Farghaly, MRCOG,

J. R. Hindmarsh, MD, FRCS, Consultant Urologist, South Cleveland Hospital, Middlesbrough.

P. H. L. Worth, FRCS, Consultant Urologist, St Peter's Hospital, London.

Requests for reprints to: S. A. Farghaly, Academic Unit, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

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Technique and Results of Trans-scrotal Operations for Hydrocele and Scrotal Cysts

R. WALDRON, M. JAMES and A. CLAIN

Department of Surgery, Dudley Road Hospital, Birmingham

Summary—Surgical procedures for scrotal hydroceles and cysts carry a significant morbidity rate from haematoma formation. Lord's transcrotal procedure involves minimal tissue dissection. The present series of 84 cases confirms Lord's original claims of a very low risk of haematoma with no recurrence.

It is concluded that Lord's procedure is effective, simple, safe and economic.

Scrotal cystic lesions are usually managed by either repeated aspiration or surgery. The use of injection techniques is controversial. Aspiration is not curative and surgery carries a significant morbidity rate from haematoma and recurrence (Shah, 1963; Efron and Sharkey, 1967). Operative procedures for scrotal hydroceles and cysts have long been a topic of controversy (Rodriguez *et al.*, 1981). All agree that a careful technique with meticulous haemostasis is mandatory if post-operative scrotal haematoma is to be avoided. In 1964, Lord described a "bloodless operation for the radical cure of idiopathic hydrocele" which basically was an opening and plication of the unmobilised tunica vaginalis. Prior to this, Solomon (1955) had reported a similar extrusion procedure whereby the edge of the tunica was sutured to its junction with the sinus epididymis. He noted that this operation was "of obscure origin" and had been demonstrated to him by S. R. Muellner of Boston at least 10 years earlier. In 1970, Lord described a "bloodless operation for spermatocele or cyst of the epididymis". Neither of these procedures has been universally adopted.

Dissatisfaction with the frequent scrotal swelling, induration and prolonged hospital stay with the more commonly used procedures led to our adoption of the Lord's procedures. In this report we describe the operative steps and review our results on 78 patients.

Patients and Methods

Seventy-eight males, ranging in age from 33 to 76 years and with single or bilateral hydroceles or scrotal cysts, were operated on between 1970 and 1984. Lord's procedures were performed for idiopathic hydrocele (51 cases), spermatocele (17) and epididymal cyst (16). Bilateral procedures were performed for six patients. In nine patients Lord's procedure was combined with a further non-scrotal operation. The operations were performed both by a consultant (45 patients) and by various surgeons in training (39). Hospital stay ranged from 1 day to 14 days, with a mean of 3 days for Lord's procedure alone (69) and 6 days for combined procedures.

In this series general anaesthesia was used, but as shown by Kaye *et al.* (1983), local anaesthesia by spermatic cord block is equally effective. The operative procedures for hydrocele and for the group of epididymal cysts and spermatoceles (scrotal cysts) are similar in the first and last stages. For either operation, the scrotum is grasped in the left hand, stretching the scrotal skin. A 4-cm incision (average length), avoiding superficial vessels, exposes the tunica and any bleeding is controlled with electrocoagulation (Fig. 1). The wound edges are then grasped with Allis's forceps and in the case

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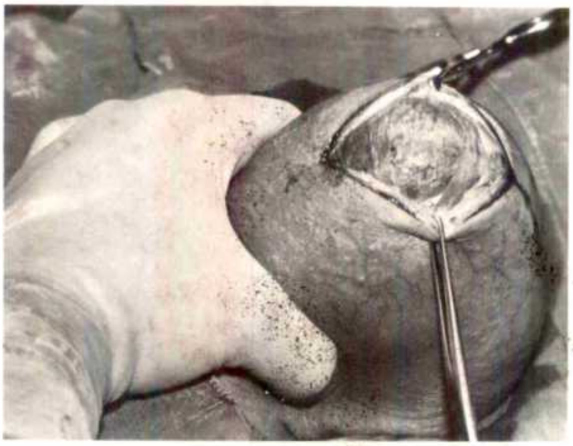

Fig. 1 The skin incision has been made after grasping the scrotum in the left hand (right-handed surgeon) and the hydrocele sac or scrotal cyst has been exposed. Allis's forceps are applied to evert the skin and dartos muscle.

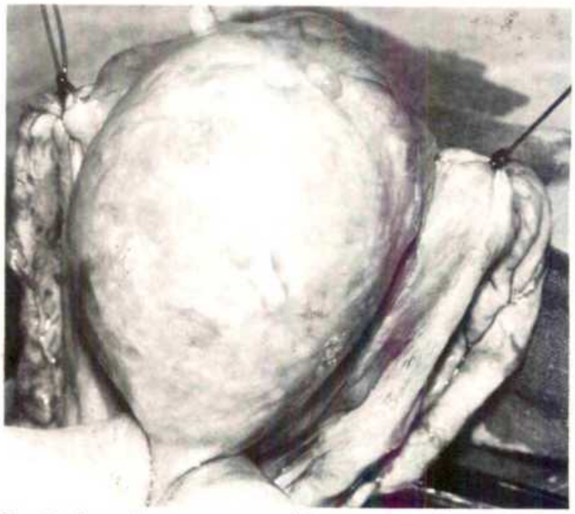

Fig. 3 Stay plication sutures of fine catgut are inserted above and below.

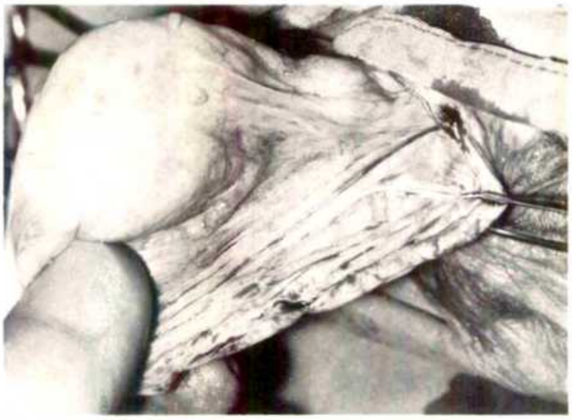

Fig. 2 The hydrocele fluid has been evacuated and the sac has been everted preparatory to inserting plication stitches. Note that the scrotal cavity has not been opened in any way.

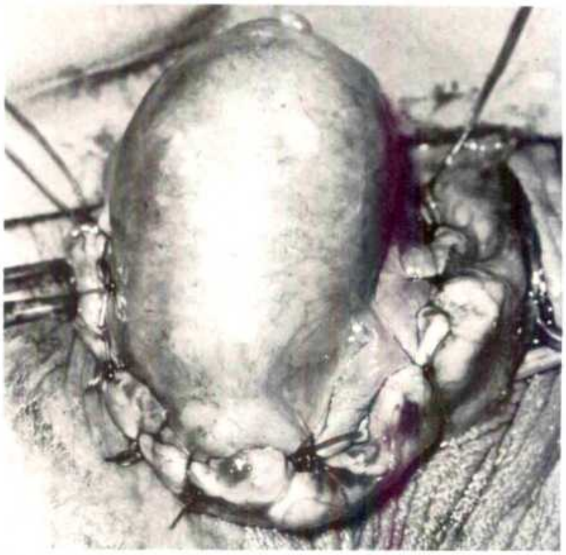

Fig. 4 An encircling series of plication sutures has been inserted; it remains to cut the two stay sutures.

of a hydrocele the sac is emptied by incising the tunica horizontally at its midpoint. The hand grip is then released and the testis is evaginated through the incision, thus turning the sac inside out (Fig. 2). The sac is not dissected out of the scrotum nor is any part of it resected. It is convenient to insert stay plication sutures above and below (Fig. 3). Small bites are then taken at 1-cm intervals, using 2/0 chromic catgut sutures from the free edge of the tunica to its junction with the epididymis and testis in an in-and-out fashion. Eight to 12 equidistant sutures are inserted and tied, thus plicating the tunica into a collar around the junction with the testis and epididymis (sinus epididymis), thereby obliterating the sac (Fig. 4). The testis is then returned to the scrotum. With a large hydrocele it may prove difficult to return the bulky plicated hydrocele and its testis to the scrotum and it may be necessary to extend the skin incision to accomplish this.

For scrotal cysts the operation is varied after the incision through the skin and dartos which exposes the cyst. The objective of this procedure is to enter the avascular plane immediately surrounding the

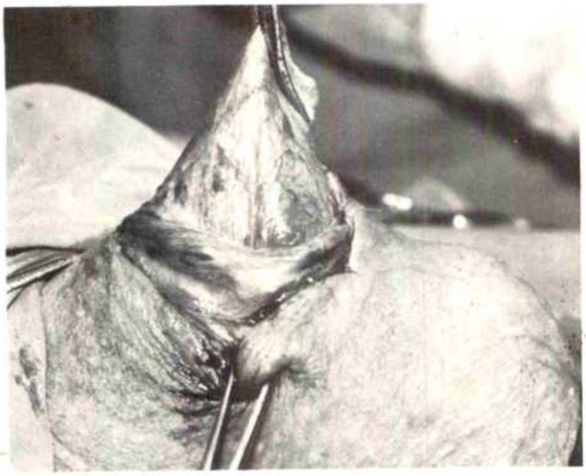

Fig. 5 The scrotal cyst has been half emptied of its fluid and grasped with a haemostat.

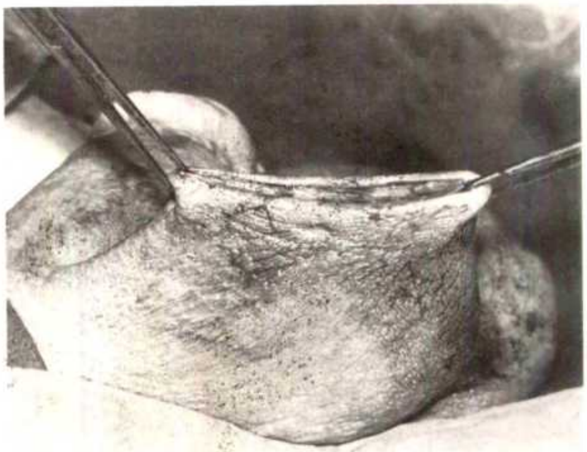

Fig. 7 The scrotal skin is put on the stretch by grasping the ends of the incision with Allis's forceps.

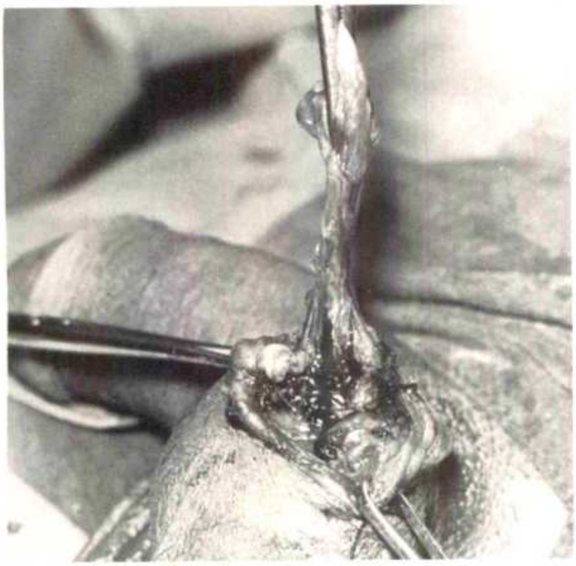

Fig. 6 The pedicle of a scrotal cyst awaits ligation with catgut.

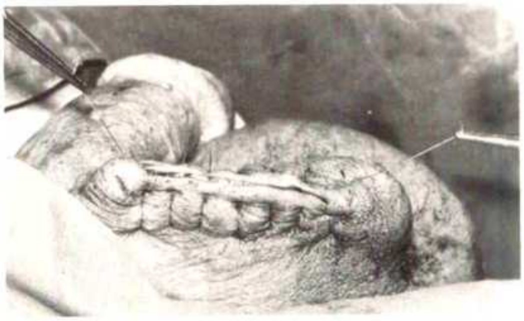

Fig. 8 The near and far catgut skin sutures should evert the scrotal skin adequately, thereby eliminating "dead space". The stay sutures placed first at the ends of the incision remain to be cut.

cyst. Most of the cyst fluid is then aspirated with a syringe, leaving about half of the fluid to facilitate dissection of the lax cyst which is grasped with an artery forceps (Fig. 5). The cyst is then delivered intact by blunt dissection of the avascular plane, ligating the final attachment of the cyst which invariably contains a blood vessel (Fig. 6). A difficulty peculiar to scrotal cysts may arise at this point. These cysts are frequently either multilocular or multiple and the scrotal cavity is often opened up to a greater extent than with the corresponding operation for hydrocele. The operation is thus sometimes more difficult than the operation described above.

The final steps in either operation are identical. The ends of the skin incision are grasped with Allis's forceps (Fig. 7). Near and far interrupted skin sutures of 2/0 plain catgut are inserted, the deep component of the suture being placed at the bottom of the skin flaps which have been raised by removing the fluid in the scrotum (Fig. 8). No drains were used in this series. After spraying the scrotal skin with "Nobecutane" a thin gauze dressing is applied and a scrotal support left on for a week. The patient should be out of bed on the day of the operation.

At follow-up 2 or 3 weeks later, in the case of a large hydrocele the plicated sac is usually still palpable but in other cases, apart from minimal induration, the scrotum feels normal. In the first category the palpable sac becomes impalpable over a period of 2 or 3 months.

Results

The patients were monitored carefully for early and late complications, focusing on haematoma, infection and recurrence. Post-operative haematoma complicated surgery in two patients following hydrocelectomy, but did not necessitate further exploration. Two patients developed a wound infection which responded rapidly to antibiotics. These patients have been followed up for 6 months to 13 years (mean 6 years) and there have been no recurrences. The mean follow-up for the three groups was as follows: 6 years for hydroceles, 8 years for spermatoceles and 5 years for epididymal cysts. The reason for a relatively long follow-up with many patients was that some were cancer cases in whom a scrotal swelling was incidental.

Discussion

The need for an improved operative procedure for scrotal hydroceles and cysts is obvious from the data reported by Maloney (1975), with a complication rate of 17% for haematoma, 10% for sepsis and an average hospital stay of 5 days. The standard procedures for hydrocele, such as radical excision (Andrews, 1907) and the Jaboulay (1902) operation, involve mobilisation of the sac and frequently result in a scrotal haematoma. Because of the limited dissection with Lord's procedures there is a minimal amount of tissue trauma; this reduces the risk of haematoma and so a drain is not necessary, thus avoiding its potential risks. Lord's operations are effective in so far as a recurrence did not occur in this series. They are simple and safe in that they may be performed equally well both by consultants and surgeons in training with minimal complications. With the present economic conditions and bed scarcity, the 3-day hospital stay rate in this series has obvious implications for day case surgery (Kaye *et al.*, 1983). In fact these operations can be performed as day case procedures. At this hospital, although there is a day case unit, pressure on beds has not made this necessary. The only deterrent to these procedures is a thick walled hydrocele rarely seen nowadays, where resection of the sac is the operation of choice. Our favourable results compare with those of others (Dahl *et al.*, 1972; Hass *et al.*, 1978).

We believe that Lord's procedures are effective, simple, safe and economic operations for scrotal hydroceles and cysts. The advantages are based on the fact that minimal dissection is required, resulting in less frequent post-operative swelling, bleeding, induration and infection.

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The Authors

R. Waldron, MCh, FRCSI, Registrar in General Surgery.
M. James, MB,BCh, House Officer in General Surgery.
A. Clain, MB(Cape), FRCS, Consultant Surgeon.

Requests for reprints to: R. Waldron, Department of Surgery, Dudley Road Hospital, Dudley Road, Birmingham B18 7QH.

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Current Optimum Management of Anaplastic Germ Cell Tumours of the Testis and Other Sites

E. S. NEWLANDS, K. D. BAGSHAWE, R. H. J. BEGENT, G. J. S. RUSTIN, S. M. CRAWFORD and L. HOLDEN

Department of Medical Oncology, Charing Cross and Westminster Medical School, London

Summary—Between 1977 and 1985, 149 male patients with anaplastic germ cell tumours (AGCT) completed chemotherapy with POMB/ACE (platinum, vincristine (oncovine), methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide). By increasing the number of courses of POMB in 1979, we have been able to compensate for adverse prognostic factors. Since then each patient has received at least three courses of POMB and 118 patients have completed therapy. The overall survival rate since 1979 is 89% and for the 100 patients who had not received prior radiotherapy it is 92%.

We established that an initial serum concentration of human chorionic gonadotrophin (HCG >50,000 iu/l) and/or alphafetoprotein (AFP >500 ku/l) indicated a poor prognosis. Between 1977 and 1979 the survival rate in 12 patients in this category was only 45%. After increasing the number of courses of POMB, the survival rate rose to 89% in 31 patients. However, patients who had received prior radiotherapy and who presented with high tumour markers (HCG >50,000 iu/l and/or AFP >500 ku/l) continue to have a poor survival rate (20% in five patients).

With this chemotherapy, 14 of 16 patients (88%) presenting with liver metastases and 6 of 7 patients (86%) presenting with brain metastases are in complete remission. Neither the stage at presentation nor the volume of metastatic disease was a major adverse prognostic variable. We believe that POMB/ACE chemotherapy, followed by surgery in selected cases, is currently the best treatment for patients with AGCT.

Anaplastic germ cell tumour is a term proposed by us to describe the biologically most aggressive histological variants of germ cell tumours and includes embryonal carcinoma, yolk sac and choriocarcinoma, and mixed tumours including any of these elements (Paradinas, 1983). It excludes mature teratomas and pure seminomas. We believe that this term is preferable to the currently widely used "non-seminomatous germ cell tumours".

The importance of germ cell tumours of all types has increased, since with appropriate therapy it should now be rare for patients to succumb from their disease. The incidence of germ cell tumours in the male is increasing and until recently they were the most common fatal cancer in men aged between 25 and 34 years (MacKay and Sellers, 1966; Davies, 1981). This increase has occurred in Europe, North America and Japan and the cause remains obscure, but one interesting possibility is exposure of the male fetus to exogenous oestrogens and progestogens taken by the mother during pregnancy (Depue *et al.*, 1983).

Over the last decade there have been major advances in the chemotherapy of AGCT. Einhorn and Donohue (1977) introduced cisplatin in combination with vinblastine and bleomycin (PVB) and in their original group the survival rate was 64%. Many other centres have adopted PVB as "standard" therapy for all patients with this disease. Stoter *et al.* (1984) reported the results of PVB

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therapy in 91 patients and their findings resemble those of Einhorn and Donohue (1977) in that 64% of their patients remained free of disease after 5 years. The Medical Research Council Testicular Tumour Working Party (1985) reported a 3-year survival rate of 71% in 179 patients treated with PVB.

Several prognostic variables have been identified in patients with AGCT, and it has been shown that the larger the volume of metastatic disease at the start of treatment the poorer the prognosis (Samuels *et al.*, 1976; Peckham *et al.*, 1977). This has been confirmed in a recent analysis of 458 patients treated at six different centres (MRC Working Party on Testicular Tumours, 1985). Hepatic and brain metastases also carried a poor prognosis in most series. Most AGCTs secrete one or more tumour markers (HCG, AFP, placental alkaline phosphatase (PLAP) and lactate dehydrogenase (LDH)). In 1980 Germa-Lluch *et al.* reported that initial serum concentrations of HCG $>10^5$ iu/l and AFP $>10^3$ ku/l were both adverse prognostic factors. This independent variable has also been confirmed in the large MRC analysis, where patients presenting with an HCG >1000 iu/l and an AFP >500 ku/l had a poorer prognosis. However, continuing analysis of our data confirms that serum concentrations of HCG >50,000 iu/l and AFP >500 ku/l discriminate most effectively between a good or a bad prognosis with POMB/ACE chemotherapy and they have been used in this analysis (Bagshawe and Begent, 1983).

It is recognised that patients with very advanced disease have a poor response to PVB and several alternatives have been examined. Vugrin *et al.* (1983) used a combination of cyclophosphamide, vinblastine, actinomycin D, bleomycin and cisplatin (VAB/6) and achieved complete remission in 91% of 36 patients. However, there were few patients with the most advanced disease in this study. Peckham *et al.* (1983) treated 43 patients with bleomycin, etoposide and cisplatin (BEP). Although 86% achieved complete remission, including 14 patients with large volume metastatic disease, no patient in that series was in the worst prognostic group, with liver or central nervous system metastases or extremely high tumour markers at the time of starting treatment. Several centres have attempted to solve this problem by using high dose chemotherapy with the complications that that entails. Ozols *et al.* (1983) used very high dose cisplatin, vinblastine, bleomycin and etoposide (PVeBV). Although the initial response rate was high with this combination, myelosuppression was also severe. Some centres have gone even further, using high dose chemotherapy with autologous marrow support; this led to four treatment-related deaths in 13 patients (Blijham *et al.*, 1981). An important feature of the series reported here is that a good survival rate can be obtained without using high dose and very toxic chemotherapy in all groups of patients, except for those who had received prior radiotherapy and had high tumour markers on referral.

We identified the significant effect of etoposide on AGCTs which had progressed after prior treatment (Newlands and Bagshawe, 1977) and have incorporated it into the primary treatment of these patients. In order to achieve stable complete remissions in patients with AGCT, a minimum dose of cisplatin is required, particularly in the poorer prognostic groups. At first we limited the total dose of cisplatin in POMB/ACE chemotherapy to 240 mg/m². An early analysis of these results (Newlands *et al.*, 1980) showed that the minimum dose of cisplatin necessary to achieve stable complete remission in most patients is 360 mg/m². These results were confirmed by Newlands *et al.* (1983) and again in the current analysis. In a randomised study, Samson *et al.* (1984) also showed that there was a dose-response effect in patients with large volume metastatic disease. In that study all patients received PVB, but those who received cisplatin 120 mg/m²/course had a significantly better survival rate than those who received cisplatin 75 mg/m²/course.

Patients and Methods

Between 1977 and 1985, 149 male patients with metastatic disease who had not received extensive prior chemotherapy have been treated. The primary sites were: testis (134); retroperitoneum (7); mediastinum (5); unknown primary site (3). Thirty patients had received prior radiotherapy (in most cases to the para-aortic nodes only) and seven had received some prior chemotherapy.

Staging

The Royal Marsden staging classification for testicular tumours has been used to describe tumour extent, site(s) and volume (Peckham *et al.*, 1979).

I. Disease limited to testis. No evidence of metastases.

IM. Disease apparently limited to testis but raised levels of tumour markers HCG and AFP following orchiectomy.

II. Para-aortic node metastases: (a) metastases <2 cm diameter; (b) metastases 2-5 cm diameter; *(c) metastases >5 cm diameter.
III. Supradiaphragmatic lymph node involvement; abdominal status (a), (b) and *(c) as above.
IV. Extra-lymphatic metastases: L1—up to three pulmonary metastases less than 2 cm in diameter; L2—more than three metastases less than 2 cm in diameter; *L3—metastases greater than 2 cm in diameter.

The stages of the patients in this series were: IM 15 (10%); para-aortic (a) and/or L1 33 (22%); para-aortic (b) and/or L2 20 (13%); para-aortic (c) and/or L3 and/or additional metastases (H+, CNS+) 81 (54%).

Patients were staged by clinical examination, chest X-ray (and, if normal, thoracic CT scan), CT scan of abdomen and, if normal, lymphangiogram or abdominal ultrasound. CNS CT scans were performed when indicated. All patients were monitored by twice-weekly serial estimations with tumour markers HCG and AFP and, if they were initially raised, LDH and PLAP. Patients presenting with serum HCG >50,000 iu/l and/or AFP> 500 ku/l are referred to as the group with high tumour markers and those with initial serum concentration at lower levels comprise the group with low markers.

Treatment

The chemotherapy schedules have been reported previously (Newlands *et al.*, 1980, 1983).

POMB
Day 1: vincristine 1 mg/m^2 intravenously; methotrexate 300 mg/m^2 as a 12-h infusion.
Day 2: bleomycin 15 mg as a 24-h infusion; folinic acid rescue started at 24 h after the start of methotrexate in a dose of 15 mg 12-hourly for 4 doses.
Day 3: bleomycin infusion 15 mg by 24-h infusion.
Day 4: cisplatin 120 mg/m^2 as a 12-h infusion, given together with hydration and 3 g magnesium sulphate supplementation (Macauley *et al.*, 1983).

ACE
Etoposide (VP16-213) 100 mg/m^2, days 1 to 5; actinomycin D 0.5 mg i.v. days 3, 4 and 5; cyclophosphamide 500 mg/m^2 i.v. day 5.

OMB
Day 1: vincristine 1 mg/m^2 intravenously; methotrexate 300 mg/m^2 as a 12-h infusion.
Day 2: bleomycin 15 mg by 24-h infusion; folinic acid rescue started at 24 h (after the start of methotrexate) in a dose of 15 mg 12-hourly for 4 doses.
Day 3: bleomycin 15 mg by 24-h infusion

The sequence of treatment schedules is two course of POMB followed by ACE. POMB is then alternated with ACE until patients are in biochemical remission as measured by HCG and AFP (and, if raised, LDH and PLAP). The usual number of courses of POMB has been three to five. Following biochemical remission, patients alternate ACE with POMB until remission has been maintained for approximately 12 weeks (Fig. 1). The intervals between each course of treatment have been kept to the minimum (usually 9-11 days). If delays are caused by myelosuppression following courses of ACE, the first 2 days of etoposide are omitted from subsequent courses of ACE.

Central Nervous System Metastases

Prophylaxis

Most patients had pulmonary metastases at presentation. Our current policy is to give CNS prophylaxis with injections of intrathecal methotrexate 12.5 mg with the first three courses of chemotherapy if the patients have pulmonary metastases and/or an initial serum concentration of HCG >1000 iu/l. Cerebrospinal fluid (CSF) concentrations of HCG and AFP were measured routinely.

Established CNS metastases

The dose of methotrexate with each course of POMB is increased to 1 g/m^2 and infused over 24 h. Folinic acid rescue starts 8 h later in a dose of 15 mg 6-hourly for 72 h. Intrathecal methotrexate in a dose of 12.5 mg is given with the courses of ACE and continued until the brain metastases have completely regressed as measured by CT scanning and CSF HCG concentrations.

Dosage reduction in patients presenting with respiratory, liver or renal failure

Rapid improvement can be obtained in these very sick patients using a combination of etoposide 100 mg/m^2 i.v. and cisplatin (EP) 20 mg/m^2 i.v. on days 1 and 2 (this can be increased to 3 days as indicated). These courses are repeated at short intervals (5-7 drug-free days) and normally the full schedule

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*H—liver involvement; *CNS+—central nervous system involvement.

* Patients defined as having advanced and bulky disease.

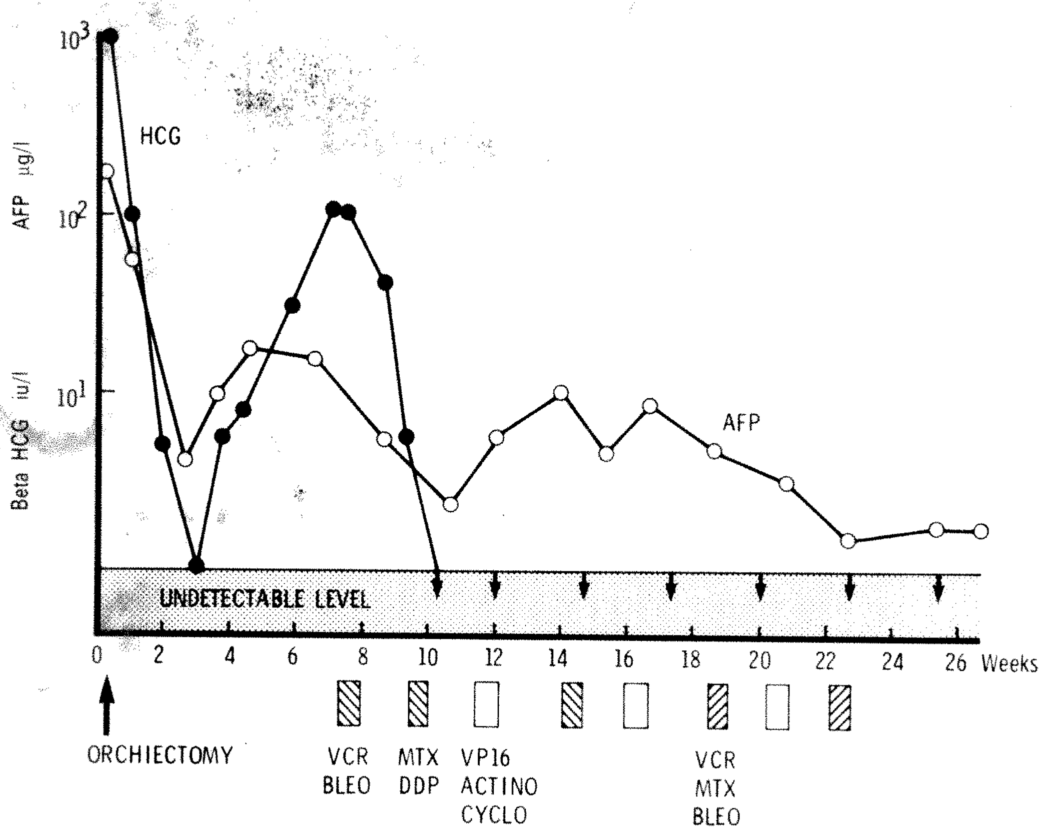

Fig. 1 Patient with minimal metastatic disease from testicular AGCT in the para-aortic region responding promptly to POMB/ACE chemotherapy by a fall in serum HCG. The baseline for AFP on this chemotherapy is often above the normal range while on therapy and falls slowly after completing treatment (Coppack *et al.*, 1983).

with POMB/ACE can be started after two or three courses of EP.

Responses

Complete response was defined as the disappearance of clinical and biochemical evidence of disease. Where CT scan revealed residual masses, these were excised where possible or biopsied. In addition, histology of resected tissue showed no evidence of active tumour.

Radioimmunoassay and life-table analysis

HCG, AFP and PLAP were measured with specific radioimmunoassays developed in this department. Survival curves were produced with the Statistical Package for Social Sciences version 7.0, in which the statistical significance of the difference between curves is assessed by the method of Lee and Desu (1972).

Results

Between 1977 and 1979, 31 patients received POMB/ACE chemotherapy, but with only two courses of POMB because at that time we were concerned about the cumulative toxicity of high dose cisplatin. The survival rate by life-table analysis in this group is 65% (Fig. 2). Since increasing the minimum number of courses of POMB to three for each patient in 1979, 118 patients have completed therapy with a survival rate of 89%, which is significantly better ($P = 0.001$). No patients were excluded because of initial extent of disease and all early deaths have been included in this report.

Multivariate analysis was performed on this large group of patients and the clinical stage of presentation has not been a major prognostic variable. POMB/ACE chemotherapy can control both hepatic and CNS metastases in most cases. Figure 3 shows the survival curve for patients with liver metastases and the survival rate is 88% in 16 patients with large volume hepatic metastases. The survival rate in patients with CNS metastases treated at this centre at the time of presentation is 86% (6 of 7 patients) and these results have been reported in detail by Rustin *et al.* (1985).

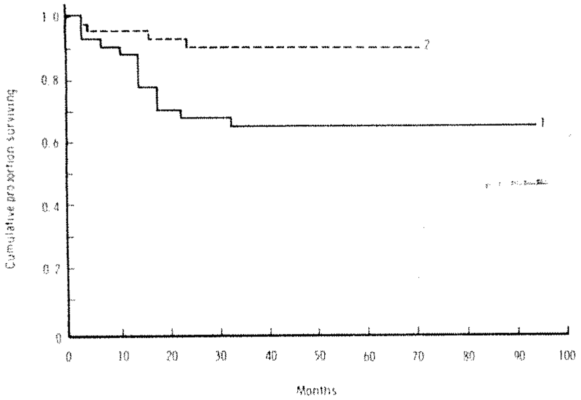

Fig. 2 Survival of patients treated for AGCT between 1977 and 1985 shows a significant improvement after increasing the minimum number of courses of POMB to three in 1979.
1 = 31 patients treated with POMB × 2 only: survival 65%.
2 = 118 patients treated with POMB × 3 or more: survival 89%.
$P = 0.001$.

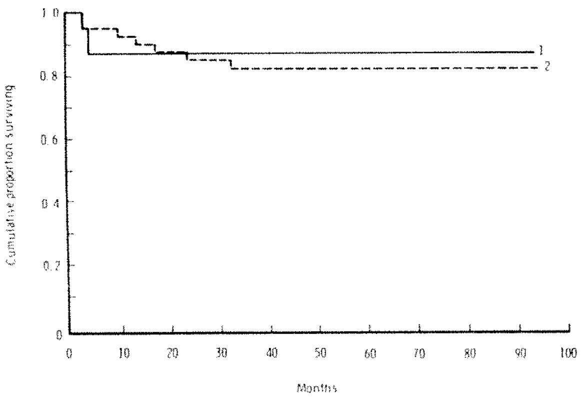

Fig. 3 Survival of patients with hepatic metastases confirming that with POMB/ACE chemotherapy this is not an adverse prognostic factor.
1 = hepatic secondaries 16 patients: survival 88%.
2 = no hepatic secondaries 133 patients: survival 83%.
$P = 0.9$.

For the series as a whole (1977-1985), the initial serum concentration of HCG and/or AFP continues to be an independent prognostic variable from the volume of metastatic disease. In Figure 4, all patients had advanced and bulky metastases in the abdomen, lung, brain or liver as defined by the staging system. In patients presenting with initial serum HCG concentration >50,000 iu/l and/or AFP >500 ku/l, the survival rate in 41 patients was 64%. In contrast, the survival rate in 40 patients presenting with tumour markers at lower concentrations was 90% ($P = 0.008$).

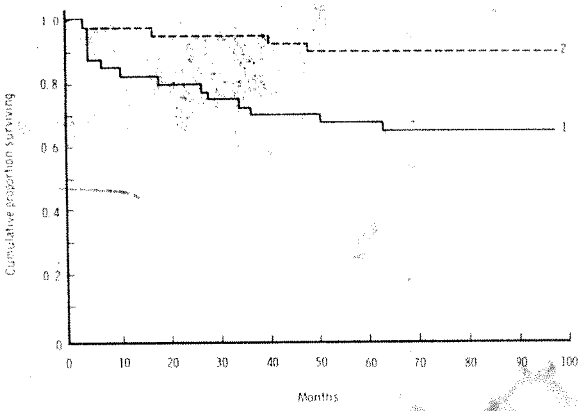

Fig. 4 Survival of patients with advanced metastatic disease.
1 = 41 patients with initial HCG >50,000 iu/l and/or AFP >500 ku/l: survival 64%.
2 = 40 patients with initial HCG <50,000 iu/l and/or AFP <500 ku/l: survival 90%.
$P = 0.008$.

Prior radiotherapy (usually to the para-aortic nodes) confers a major adverse prognosis in patients who subsequently relapse with high tumour markers. In patients presenting with high markers who had not received prior radiation we have compensated for the aggressive biological behaviour of the tumour by increasing the number of courses of POMB. Between 1977 and 1979, the survival rate in patients presenting with an HCG >50,000 iu/l and/or AFP >500 ku/l was only 45% in 11 patients. Having recognised the poor prognosis in this group, the modification in treatment since 1979 has resulted in an improvement in survival to 89% in 31 patients. This difference is significant ($P = 0.0033$). Patients who had received prior radiotherapy and who presented with low tumour markers have survived well throughout the series (83% of the patients treated between 1977 and 1979 and 92% of those treated between 1979 and 1985). In contrast, Figure 5 illustrates the survival rate of patients who had received prior radiation and were referred with high tumour markers (HCG and/or AFP) at the time of starting POMB/ACE chemotherapy. The numbers are small but it is clear that this subgroup accounts for a significant part of the mortality in this series. Figure 6 illustrates the current survival curve of 92% in 100 patients treated since 1979 who had received no prior radiotherapy.

The toxicity of POMB/ACE chemotherapy is predictable. The principal toxicity from POMB is usually limited to the nausea and vomiting associated with high dose cisplatin. Some patients developed high frequency hearing loss on audiogram

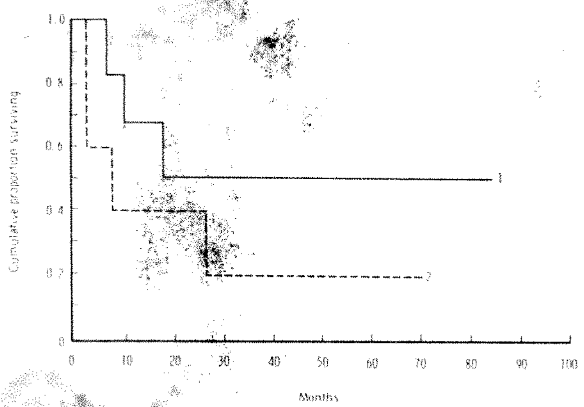

Fig. 5 Survival of patients who had received prior radiotherapy and were referred with high tumour markers (HCG and AFP).
1 = 6 patients treated 1977-1979: survival 50%.
2 = 5 patients treated 1979-1985: survival 20%.
$P = 0.22$.

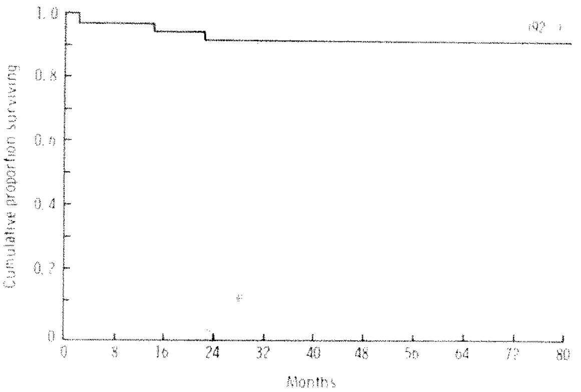

Fig. 6 Survival of patients with AGCT treated between 1979 and 1985, excluding those who had received prior radiotherapy.

when cisplatin was given as a short intravenous infusion. This problem has been less since cisplatin has been administered as a 12-h infusion. Peripheral neuropathy also occurs but this is usually reversible. Biochemical renal damage occurs in some patients but usually recovers after completing therapy. Courses of ACE induce more myelosuppression and in some patients subsequent courses of ACE are reduced to 3 days (omitting the first 2 days of etoposide). The haematological toxicity has been previously reported (Newlands *et al.*, 1980); approximately one-quarter of patients develop fever associated with neutropenia and they have been treated with broad spectrum antibiotics (initially ticarcillin and, more recently, pipracillin combined with tobramycin).

Discussion

The primary aim of treatment of patients with metastatic AGCT is to obtain complete stable remissions in the maximum number of patients during primary therapy. It is surprising that so many centres have failed to recognise the great difficulty in achieving second complete remissions after primary drug treatment has failed. AGCTs can develop either relative or total drug resistance if they are not eliminated rapidly. This problem is clearly shown by the difficulty we experienced in salvaging patients who failed on prior therapy with either vinblastine and bleomycin or PVB. In these patients, who will be reported separately, we have been able to salvage only half with a variety of modifications of POMB/ACE chemotherapy and, in many cases, surgery. The problem of inducing drug-resistance makes it imperative that patients receive the optimum therapy from the start. There are also potential problems in attempting to reduce toxicity since this can also reduce efficacy. In a study reported by Peckham *et al.* (1985), three of 17 patients with small volume metastatic disease treated only with etoposide and cisplatin developed drug resistance and progressive disease.

Sequential POMB/ACE chemotherapy has several advantages over apparently simpler drug schedules such as PVB. A regimen that does not include cisplatin with each course of therapy is more acceptable to the patient. Patients with minimal metastatic disease receive only three courses of cisplatin, which is the most unpleasant drug included in virtually all current schedules for treating AGCT. The limited myelosuppression from courses of POMB permits the intervals between each course of chemotherapy to be kept to a minimum (usually 9-11 days, depending on recovery from myelosuppression). We think that longer intervals between courses of chemotherapy could lead to tumour recovery and the development of drug resistance. The inclusion of seven drugs probably also diminishes the chance of developing drug resistance. The duration of therapy of POMB/ACE can be adjusted to the response in each individual, so that the patient receives sufficient courses of POMB to achieve biochemical remission. Induction therapy with etoposide and cisplatin (EP) in low dose has proven safe and useful in very sick patients. Many of these would probably have succumbed to more intensive therapy given while they were still in respiratory, hepatic or renal failure.

Many centres have reserved etoposide for use in salvage therapy after the failure of PVB. We think it is irrational not to include such an active drug in the primary therapy of patients with AGCT. The results reported here include all patients referred during the period of analysis with no exclusions for extent of disease. The only series with a comparable survival rate is that of Logothetis *et al.* (1985). This smaller series also contained many patients with advanced diseases but their results were obtained at the expense of greater toxicity (45% developed neutropenic sepsis). However, their approach was similar to ours, using alternating chemotherapeutic regimens.

We have focused on the problem of high initial tumour markers (HCG and/or AFP) and have been able to compensate for this by increasing the number of courses of POMB. Except for patients who had received prior radiation and who presented with high tumour markers, the overall survival rate in 100 patients treated during this most recent period is 92%. Given that some of the early deaths in this series included patients who died from such causes as aortic perforation from tumour involvement and multiple intestinal fistulae from tumour at the time of presentation, it will be difficult to improve on this figure with currently available chemotherapy. POMB/ACE treatment is equally effective in patients presenting with AGCT from other sites. All five patients with mediastinal teratomas who had not received prior treatment have been salvaged with POMB/ACE chemotherapy combined, in most cases, with surgery. In patients with ovarian AGCT, POMB/ACE chemotherapy has been equally successful. In a recent analysis of 37 patients, the overall survival rate was 77%. However, as with their male counterparts, these tumours can rapidly become drug resistant and patients who had received prior radiation or chemotherapy had a poor prognosis. In patients who had received no prior treatment, the survival rate was 83% (Newlands and Bagshawe, 1985).

While patients with advanced seminomas respond well to POMB/ACE chemotherapy, the number of patients so treated is small. In those who present with recurrent seminomas after initial therapy with radiotherapy and/or chemotherapy, drug resistance and profound myelosuppression remain a problem in administering POMB/ACE in the intended dose and frequency. From a total of 10 such patients we have been able to salvage only five.

One facet of management of AGCT which is currently undergoing considerable discussion is the role of surgery. Our policy has been to excise residual masses at the end of chemotherapy if this is feasible. Analysis of these patients shows no increase in survival. However, this does not exclude a small number of patients who might have relapsed if surgery had not been performed (this would seem probable in some patients with particularly large volume disease, such as massive mediastinal AGCT). In most cases the tissue removed was either necrotic or differentiated teratoma. In patients where malignant tissue was still present, further chemotherapy with POMB/ACE was given post-operatively.

In many of our patients there had been a delay in diagnosis after the onset of testicular symptoms (usually testicular enlargement followed by pain and other symptoms). It is important that any patient presenting with testicular enlargement is examined with the possibility of tumour in mind. Preoperative diagnosis can be made in many cases of AGCT by sending a serum sample for analysis of tumour markers. It is gratifying that during this study the proportion of patients falling into the most advanced disease category has tended to fall, probably reflecting a greater public and medical awareness of testicular tumours.

Patients who present with stage I disease (no evidence of spread following initial orchiectomy) are staged carefully and receive meticulous follow-up (involving serum tumour markers and regular clinical and radiological assessment). This policy has permitted three-quarters of the patients to receive no additional therapy following orchiectomy. All patients who developed metastases have been salvaged with POMB/ACE chemotherapy.

Acknowledgements

We thank the surgeons and radiotherapists who referred patients and the staff at Charing Cross Hospital for their support. This work was supported by the Cancer Research Campaign and the Medical Research Council. We thank Ms P. Newman for computer analysis and Lederle Laboratories for help in data collection.

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The Authors

E. S. Newlands, PhD, FRCP, Senior Lecturer and Honorary Consultant Physician.

K. D. Bagshawe, MD, FRCP, FRCOG, FRCR, Professor of Medical Oncology.

R. H. J. Begent, MD, MRCP, Senior Lecturer and Honorary Consultant Physician.

G. J. S. Rustin, MD, MSc, MRCP, Senior Lecturer and Honorary Consultant Physician.

S. M. Crawford, MRCP, Senior Registrar.

L. Holden, MSc, Research Assistant.

Requests for reprints to: E. S. Newlands, Department of Medical Oncology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF.

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Post-treatment Fertility in Patients with Testicular Cancer

III. Influence of Radiotherapy in Seminoma Patients

SOPHIE D. FOSSÅ, T. ÅBYHOLM, N. NORMANN and V. JETNE

Department of Medical Oncology and Radiotherapy and Department of Medical Physics, Norwegian Radium Hospital; Department of Gynaecology, Rikshospitalet; Hormone Laboratory, Aker Hospital, Oslo, Norway

Summary—Sperm analysis and serum hormone measurements (LH, FSH, testosterone) were performed in 29 patients after orchiectomy for seminoma before and after irradiation. Before radiotherapy 14 of 20 orchiectomised patients were azoospermic or had impaired spermatogenesis. A minimum sperm count was found 1 year after radiotherapy with gradual improvement up to 2 years. The recovery of sperm cell production was impaired most in patients with pre-treatment sperm counts <3 million/ml.

Serum testosterone remained at low normal levels throughout the observation period. The mean serum FSH was increased 1 year after radiotherapy but returned to normal in 50% of patients within 3 years after treatment. This post-treatment increase in FSH was significantly correlated with increased pre-treatment FSH but not with the gonadal dose, which was 1 to 3% of the target dose.

Severe disturbances in spermatogenesis, observed 2 to 3 years after radiotherapy for early seminoma, are likely to be the expression of a highly impaired pre-treatment sperm cell production and only to a lesser degree dependent on the irradiation of the remaining testicle.

Radiotherapy, chemotherapy and surgery represent the main pillars in the treatment of testicular cancer. Disturbances in fertility after chemotherapy and/or surgery have been discussed previously (Fosså *et al.*, 1985a and b). This study presents the results of hormone and sperm analysis before and after radiotherapy and discusses the possible influence of irradiation on the fertility of patients with testicular cancer.

Patients and Methods

Hormone analysis alone or in combination with sperm analysis was performed before and 1 to 3 years after irradiation of 29 patients orchiectomised for seminomatous testicular cancer during 1980 and 1981 (27 stage I patients (without metastases) and two stage II patients (with retroperitoneal metastases)). Their mean age at the time of the diagnosis was 41.5 years (range 26-64).

Radiotherapy

The patients underwent abdominal irradiation to an L-field. This treatment field comprised the bilateral para-aortic and ipsilateral iliac lymph nodes (Fig. 1). Until 1981 the external inguinal lymph nodes were irradiated in those with:

(i) Previous herniotomy, orchiopexy or operation for hydrocele on the side of the testicular tumour, or
(ii) infiltration of the spermatic cord, epididymis, testicular capsule or scrotal wall.

This routine inguinal irradiation was omitted in 1981. Fourteen patients received inguinal radiotherapy and 15 did not.

Until the end of 1980 the scheduled target dose in seminoma patients was 40 Gy. From 1981 the

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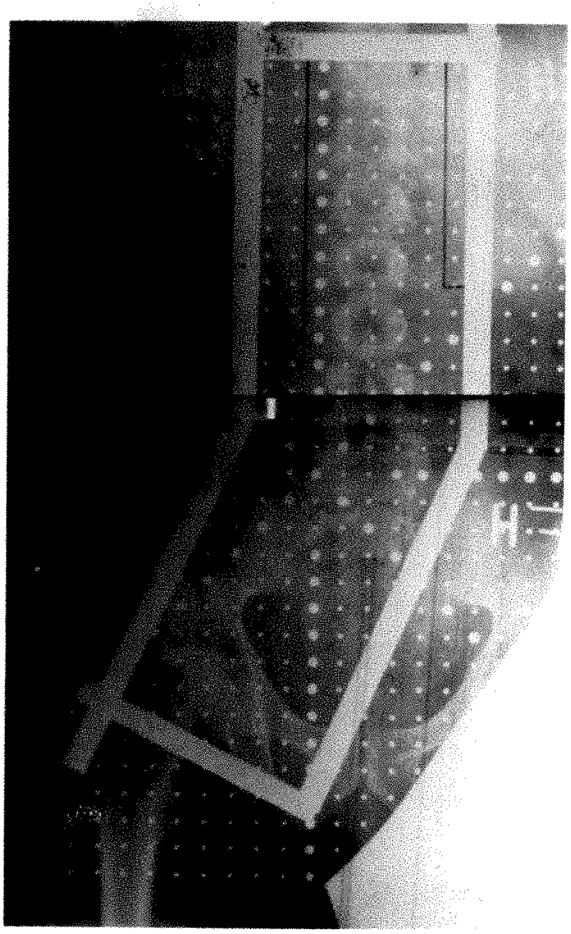

Fig. 1 L-field (without inguinal irradiation) for radiotherapy of testicular cancer.

target dose was reduced to 36 Gy for stage I patients but remained unchanged for stage II patients. Thus eight patients received 36 Gy and 22 received 40 Gy. All irradiation was delivered by a linear accelerator 7 MV X-rays to an anterior and a posterior field. Either field was treated daily. The daily dose was 2 Gy, given 5 times weekly. The groin was irradiated by an anterior field only.

Testicular shielding

The scrotum with the remaining testicle was drawn from the treatment field so that as much as possible could be shielded by a 5-cm thick lead block placed close to the scrotum. In patients aged less than 40 years the gonadal dose was measured during the first 2 to 4 daily fractions. These measurements served as the basis for calculations of the total gonadal dose. The median gonadal dose (17 patients) was 54.8 cGy (range 27-100 cGy).

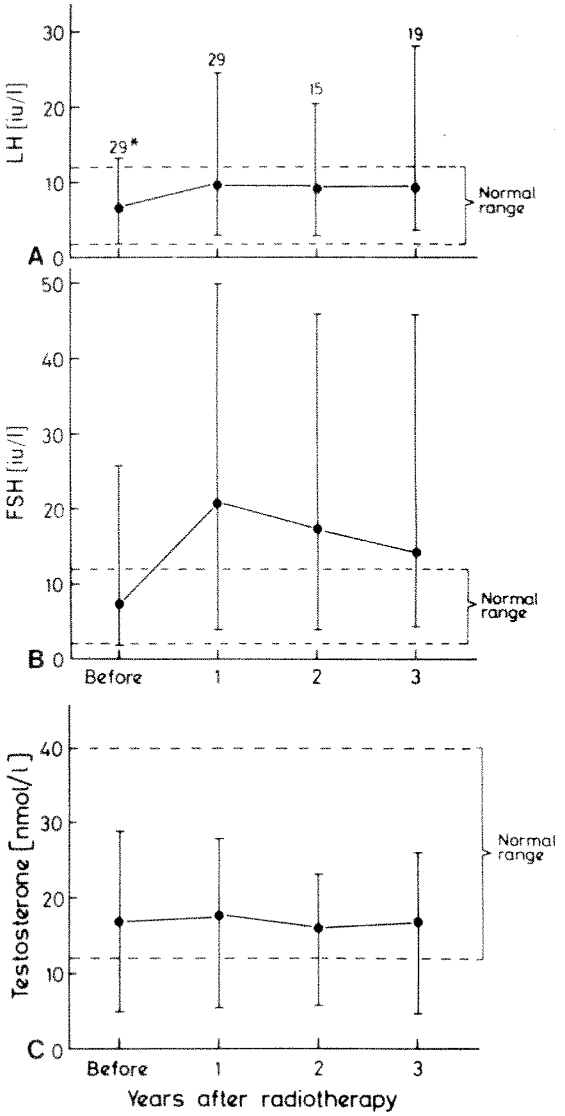

Fig. 2 Serum hormone levels (mean) in patients with testicular cancer before and 1 to 3 years after radiotherapy. (A) LH, (B) FSH, (C) Testosterone.
I: Range *: No. of patients.

Evaluation of fertility

Pre-treatment analysis of serum LH, FSH and testosterone was done in 29 patients as previously reported (Fosså *et al.*, 1980, 1984). Serum hormone analysis was repeated 1 year after radiotherapy in all 29 patients and after 2 and 3 years in 15 and 19 patients respectively. Sperm analysis was performed before radiotherapy in 20 patients. Post-treatment sperm analysis was done in 19 patients after 1 year and in 15 patients after 2 to 3 years. The results of sperm analyses were evaluated according to the number of sperm cells/ml and taking into account the sperm cell motility and morphology. Three different categories were defined: azoospermia, impaired spermatogenesis (sperm cell density < 10 million/ml and/or motility index < 20 and/or frequency of amorphous sperm cells > 80%), and normospermia.

Statistics

The chi-square test or the Fisher exact probability test was used to evaluate distributions. A difference was regarded as statistically significant if P was less than 0.05.

Results

The mean values of LH, FSH and testosterone before radiotherapy were within the normal range. Serum testosterone was below the normal range in 7 of 29 patients before radiotherapy. One year after the end of treatment the mean serum FSH was elevated, 21 of 29 individual values (68%) being above the normal range. The mean levels of LH and testosterone remained within the normal range after treatment, though most of the testosterone values were below 20 nmol/l. During the second and third year after radiotherapy there was a gradual decrease in the mean FSH, but without a complete return to normal levels within the first 3 years after therapy. After 3 years, 9 of 19 patients still had elevated serum FSH values, 6 of them above 20 nmol/l. The elevation in FSH for 2 to 3 years after treatment was significantly correlated with the increase in FSH before treatment (Table 1) ($P = 0.03$).

The median sperm cell density before treatment was 9×10^6/ml (Fig. 3). The lowest levels were reached 1 year after radiotherapy, followed by a gradual increase in the mean and median number of sperm cells/ml during the following 2 to 3 years. Only 6 of 20 patients were normospermic before radiotherapy; the others were in the group with impaired spermatogenesis. Two to 3 years after irradiation about half of the patients (7/15) were normospermic (Table 2). There was a significant correlation between sperm density before treatment and sperm density 2 to 3 years after treatment, the discrimination line being at $> 3 \times 10^6$ sperm cells/ml (Table 3) ($P = 0.03$). In 3 of 4 patients who before radiotherapy had extremely low sperm cell counts ($\leqslant 3 \times 10^6$), the sperm cell density remained low during the 2 to 3 years' observation period, whereas all six patients with pretreatment sperm cell counts $> 10 \times 10^6$/ml had regained sperm cell densities $> 10 \times 10^6$/ml after this time (Table 3).

Table 1 FSH Levels Before and 2 to 3 Years After Treatment

	Number of patients		
	Post-treatment FSH		
Pre-treatment FSH	*Normal*	*Elevated*	*Total*
Normal	13	7 (3)	20
Elevated	0	4 (4)	4
Total	13	11 (7)	24

(Normal: ≤ 12 u/l) $P = 0.03$). () Number of patients with post-treatment FSH > 20 u/l.

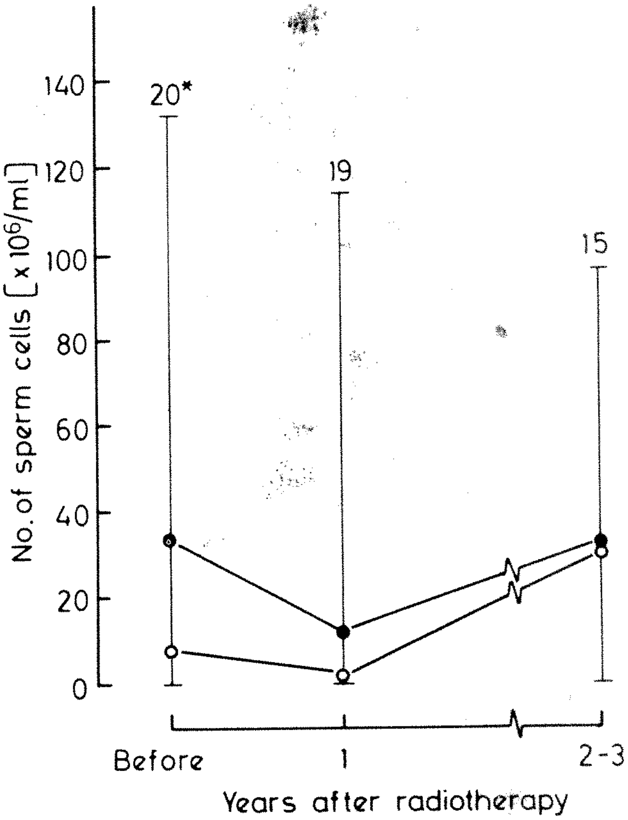

Fig. 3 Sperm cell density in patients with testicular cancer before and 1 to 3 years after radiotherapy.
●–●: Mean ○–○: Median *: No. of patients
I: Range

No significant correlation, merely a tendency ($P = 0.3$), was found between the gonadal dose and the post-treatment increase in FSH (after 2-3 years) (Table 4). The gonadal dose itself was only slightly

Table 2 Sperm Analysis Before, 1 and 2 to 3 Years After Radiotherapy for Testicular Cancer

	Number of patients			
Years before/after radiotherapy	*Azoo-spermia*	*Impaired spermato-genesis*	*Normo-spermia*	*Total*
Before	1	13	6	20
1	6	9	4	19
2-3	2	5	8	15

Table 3 Pre-treatment Sperm Counts vs Sperm Counts 2 to 3 Years After Radiotherapy

	Number of patients			
	Post-treatment × 10^6*/ml*			
Pre-treatment × 10^6*/ml*	*Total*	*0-3*	*4-10*	*>10*
0-3	4	3	0	1
4-10	5	1	1	3
>10	6	0	0	6

($P = 0.03$)

Table 4 Gonadal Dose and FSH Levels 2 to 3 Years after Treatment

	Number of patients		
	Post-treatment FSH		
Gonadal dose (cGy)	*Normal*	*Elevated*	*Total*
≤50	4	2	6 (2)
>50	3	6	9 (3)
Total	7	8	15 (5)

(Normal ≤12 u/l) ($P = 0.31$). () Number of patients with post-treatment FSH >20 u/l.

related to whether or not inguinal irradiation was given ($P = 0.31$) (data not shown).

Discussion

The effect of ionising radiation on spermatogenesis has been studied previously (Sandeman, 1966; Rowley *et al.*, 1974; Kuber *et al.*, 1980; Greiner, 1982; Hahn *et al.*, 1982; Berthelsen, 1984). Depending on the gonadal dose, azoospermia was observed 3 to 6 months after completion of irradiation, with a subsequent gradual improvement in spermatogenesis noted in most patients, starting 9 to 12 months after radiotherapy. In most previous studies only the sperm count has been used as a measure of spermatogenesis. In the present study serum FSH was also measured, since a close relationship between FSH levels and spermatogenesis has been shown previously (Pryor *et al.*, 1976).

The present study confirms previous observations that only one-third of patients with seminoma have normospermia after unilateral orchiectomy before further treatment (Berthelsen, 1984; Fosså *et al.*, 1984). However, the present results also demonstrate that impaired sperm cell production shortly after orchiectomy (and before further treatment) is reversible in about half of the patients: in 4 of 9 patients with pre-treatment sperm counts $\leqslant 10 \times 10^6$/ml, higher values were found 2 to 3 years after irradiation.

In general, it is believed that the gonadal dose is the most important factor in the post-treatment impairment of sperm cell production (Greiner, 1982; Hahn *et al.*, 1982). Contrary to this but in accordance with the observations of Berthelsen (1984), we found no significant correlation between gonadal dose and post-treatment sperm cell production evaluated as the number of the patients with increased FSH 2 to 3 years after radiotherapy. This may be due to several reasons:

(1) The gonadal dose was based on the dosimetric results obtained during the 2 to 4 initial daily fractions. These single measurements may not always be representative of the total gonadal dose. Day-to-day variations in the gonadal dose are difficult to avoid in routine radiotherapy, due mainly to the varying position of the remaining testicle during the daily fraction.

(2) Pre-treatment disturbances in spermatogenesis are strongly correlated with the post-treatment results of sperm analysis. Patients who are azoospermic or severely oligozoospermic before treatment, or have elevated FSH levels before radiotherapy, tend to maintain low sperm counts and/or elevated FSH values after radiotherapy. This is likely to be evidence of abnormal pre-treatment spermatogenesis and relatively independent of the gonadal dose, as long as this is below 100 cGy. Thus, low sperm counts found in patients 2 to 3 years after radiotherapy are not always due to a high gonadal dose but may be the expression of a pre-treatment disturbance in spermatogenesis in the individual patient. When evaluating the real influence of the gonadal dose, only patients with normal pre-treat-

ment spermatogenesis and/or normal serum FSH should therefore be considered.

(3) Conventional sperm analysis is not accurate and there are considerable variations between individuals and observers (Belsey *et al.*, 1980; Jequier and Ukombe, 1983), especially in oligozoospermic patients.

Nevertheless, it seems desirable to keep the gonadal dose as low as possible (Greiner, 1982; Hahn *et al.*, 1982). This is achieved by proper shielding of the remaining testicle (Kuber *et al.*, 1980; Kubo and Shipley, 1982). During the daily fraction the distance between the remaining testicle and the treatment field should be increased as much as possible. Furthermore, high target doses and unnecessary irradiation of the external inguinal lymph nodes should be avoided. For irradiation of seminoma stage I, a total dose of 30 to 36 Gy is sufficient. The groin should be irradiated only if there is evidence of metastases in this region. By following these rules the gonadal dose can be kept at 1 to 3% of the target dose.

In many cases sperm production has recovered, at least partly, about 1½ to 2 years after irradiation and post-radiotherapy paternity has been described by Sandeman (1966), Smithers *et al.* (1973) and Hahn *et al.* (1982). In addition, it is generally recommended, according to genetic considerations, that patients should not father a child until at least 1 year after radiotherapy (Russell, 1954).

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The Authors

Sophie D. Fosså, MD, PhD, Consultant in Radiotherapy and Medical Oncology, Norwegian Radium Hospital.

T. Åbyholm, MD, PhD, Consultant Gynaecologist, Rikshospitalet.

N. Normann, FRCP(C), Head of Hormone Laboratory, Aker Hospital.

V. Jetne, MSc, Senior Physicist, Department of Medical Physics, Norwegian Radium Hospital.

Requests for reprints to: Sophie D. Fosså, Norwegian Radium Hospital, Montebello, 0310 Oslo 3, Norway.

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Further Evidence of Venous Outflow Restriction During Erection

K.-P. JUENEMANN, J.-A. LUO, T. F. LUE and E. A. TANAGHO

Department of Urology, University of California School of Medicine, San Francisco, USA

Summary—To elucidate the effect of venous outflow restriction during erection, we studied eight dogs during artificial saline perfusion of the penis with and without neurostimulation to induce erection.

With the infrarenal aorta clamped temporarily, saline infusion rates of 0.9 and 1.9 ml/min raised the mean intracorporeal pressure to 34 and 42 cm H_2O, respectively, before stabilisation or return to baseline. When cavernous nerve stimulation was initiated, the mean intracorporeal pressure rose to 124 and 184 cm H_2O (with infusion rates of 0.9 and 1.9 ml/min respectively) to induce full erection.

Our results show that venous outflow restriction takes place during erection and that it is necessary not only to induce full erection but also to maintain it. Evaluation of venous competence is therefore essential during the investigation of impotence.

Although increased arterial inflow is recognised as a major contributing factor to penile erection in humans and animals (Newman *et al.*, 1964; Virag, 1982; Lue *et al.*, 1983a; Juenemann *et al.*, 1985), the importance of venous flow restriction was largely ignored until Wagner's observations in humans (Wagner, 1981) and our studies in animals (Lue *et al.*, 1983a, b; Juenemann *et al.*, 1985). Indeed, considerable controversy still exists because of the conflicting results from the human penile perfusion studies of Newman and Reiss (1984) and the radioisotope work of Shirai *et al.* (1976).

Perfusion of the cavernous tissue with normal saline was originally used to study the arterial inflow during artificially induced erection (Michal and Pospichal, 1978) and it became a further diagnostic tool for evaluation of organic impotence (Virag *et al.*, 1984). We have demonstrated that an active reduction in intracorporeal venous capacity takes place during papaverine-induced erection (Juenemann *et al.*, 1985). In the present report we studied the venous outflow system exclusively by clamping the infrarenal aorta during saline perfusion of the corpora cavernosa in the presence and absence of neurostimulation.

Materials and Methods

In eight mongrel dogs, weighing 24 to 35 kg, anaesthesia was induced by premedication with acepromazine (0.5 mg/kg BW) and ketamine (5.0 mg/kg BW) subcutaneously and subsequent intravenous administration of sodium pentobarbital (45- to 60-mg boluses) to maintain an adequate level of anaesthesia and spontaneous respiration. Fluid maintenance consisted of intravenous normal saline (2 ml/kg/h). Surgery was performed as follows. Through a midline incision the entire penis was denuded, exposing both corpora cavernosa completely. Two 19-gauge butterfly needles were placed into each corpus cavernosum, one proximally for intracorporeal pressure recording (Statham pressure transducer) and one distally for controlled saline perfusion (Harvard perfusion pump). Systemic blood pressure was recorded through a 16-gauge cannula placed in the right femoral artery. In addition, a cuff-electrode (Avery Laboratories) was placed around the cavernous or pelvic nerve unilaterally to induce erection by stimulation of the

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Table Intracorporeal Response to Saline Perfusion Without and With Neurostimulation*

Infusion rate (ml/min)	*Baseline pressure Mean/range (cmH$_2$O)*	*Peak pressure Mean/range (cm H$_2$O)*	*Pressure rise above baseline (cm H$_2$O)*	*Total volume to reach peak Mean/range (ml)*
0.9	18.3/12–36	34.0/12–96	15.7	1.1/0.3–2.0
1.9	14.3/12–16	42.2/12–92	27.8	4.0/2.1–7.0
With Neurostimulation†				
0.9	18.3/12–36	124.3/12–228§	107.2	4.1/2.2–5.65
1.9	14.3/12–16	183.7/110–228	169.4	11.8/6.3–21.3

* Each experiment was performed with six dogs and the infrarenal aorta was clamped throughout the experiment.

† 4–7 V; 33 Hz.

§ No further recording possible (off scale).

nerve bundle (4–7 V, 33 Hz [0.5 V, 20 Hz in one dog]). By placing a Statinsky clamp on the infrarenal aorta during intracorporeal perfusion with normal saline at a constant rate (0.9 or 1.9 ml/min), the arterial factor was eliminated. Once all monitoring and stimulating devices were in place, the animal was anticoagulated with sodium heparin (2000-u bolus intravenously) and maintained with 50 u/h to ensure that the pressure recording cannula did not become obstructed with blood clots. Perfusions were performed both with and without neurostimulation. After each perfusion study, the clamp was released for at least 10 min to allow adequate blood perfusion and recovery of the erectile tissue before the next perfusion or neurostimulation experiment was begun.

Of the eight animals, six were perfused with a flow rate of 0.9 ml/min; four of these were studied a second time with a perfusion rate of 1.9 ml/min, as were the two other dogs (for a total of six dogs for each experiment).

Results

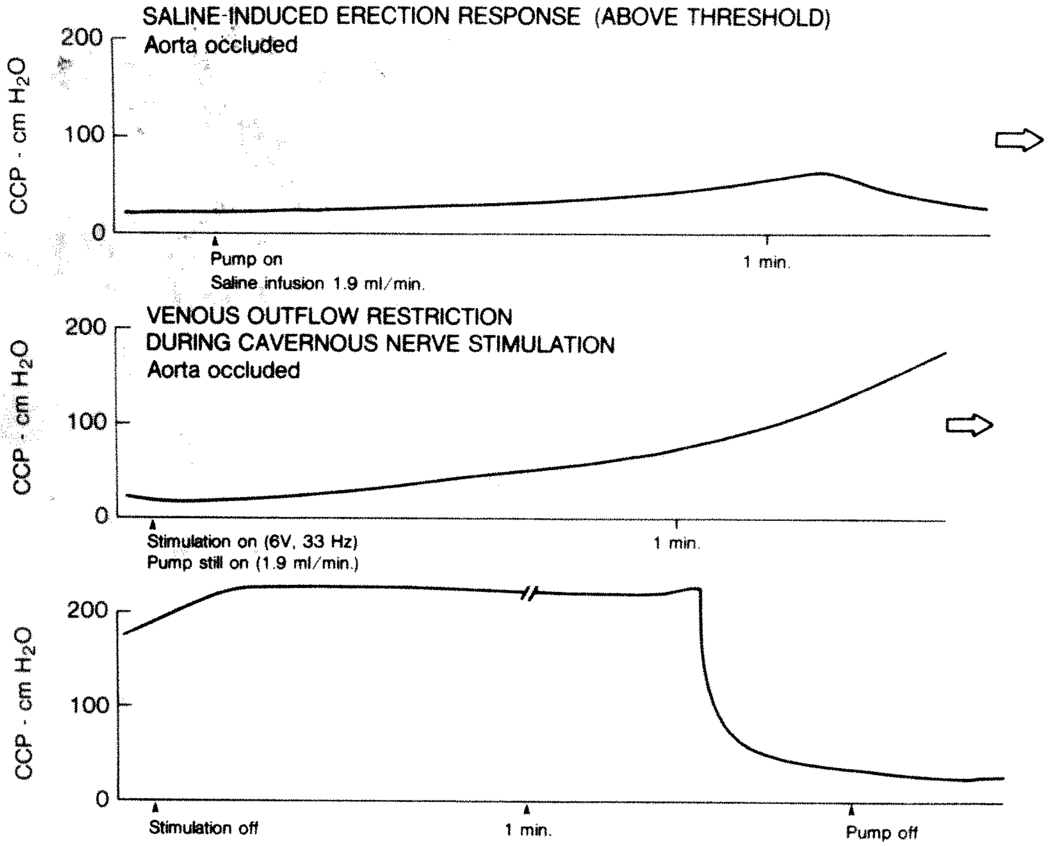
Saline Perfusion Alone

To elucidate the effect of normal saline infusion on the venous outflow system, the corporeal pressure response to the two different perfusion rates (0.9 and 1.9 ml/min) was noted. The mean values (ranges) of baseline and peak pressures as well as the infusion volume needed to attain the highest pressure level are listed in the Table.

Three of the six animals perfused with 0.9 ml/min showed no corporeal pressure change, but they responded significantly differently when the cavernous nerve was stimulated (*vide infra*). With saline infusion, the corporeal pressure went up to an average peak level of 34 cm H_2O (12-96 cm H_2O), which corresponds with an average pressure rise above baseline of 15.7 cm H_2O. An average volume of 1.1 ml saline was necessary to attain peak pressure. Once the high-pressure plateau had been achieved the pressure stabilised or, if the peak was >50 cm H_2O, the pressure gradually dropped to close to the baseline value. This effect was observed in all perfusion studies when the pressure rose above 50 cm H_2O, even with the higher flow rate of 1.9 ml/min (Fig. 1, top). The pressure increases in response to the higher rate were slightly different from the low flow results, and the peaks were slightly higher. Only one dog did not respond to the 1.9 ml/min infusion but, again, the pressure rose significantly with neurostimulation.

Neurostimulation During Saline Perfusion

Once the pressure had stabilised or returned to baseline and no further pressure change was noted, stimulation of the cavernous nerves was initiated. Immediately the corporeal pressure dropped slightly for about 5 to 10 s, then increased rapidly in proportion to the flow rate as well as the current (the lower the flow rate and current, the longer it took to achieve full erection or the peak pressure point). The highest pressure levels achieved were >228 cm H_2O for both flow rates, with an average peak of 124 cm H_2O for 0.9 ml/min and 184 cm H_2O for 1.9 ml/min (Table and Fig. 1). The mean pressure rise above baseline was about 683% greater at 0.9 ml/min than that attained without neurostimulation and about 609% greater at 1.9 ml/min. The peak values may be even higher because the pressure recording needle went off the scale when 228 cm H_2O had been reached (110 cm H_2O once). When this happened, the neurostimulation and perfusion were terminated, and it took about 1.5 to >3.5 min for the pressure to return to baseline. Even when neurostimulation was termi-


SALINE-INDUCED ERECTION RESPONSE (ABOVE THRESHOLD)
Aorta occluded

VENOUS OUTFLOW RESTRICTION
DURING CAVERNOUS NERVE STIMULATION
Aorta occluded

Fig. 1 Representative response in one dog to perfusion of normal saline at 1.9 ml/min (the "above-threshold" rate). *Top:* Note the drop after the peak pressure point is achieved. *Middle and Bottom:* Pressure response within the same corpus cavernosum during neurostimulation of the cavernosus nerve and constant saline perfusion. Note the tremendous pressure rise due to stimulation-induced venous outflow restriction of the corpora cavernosa. Once the stimulator is switched off, the dog is unable to maintain the erection with this perfusion rate. (CCP = corpus cavernosum pressure).

nated before the pressure gauge went off the scale (even at 50 cm H_2O below this critical level), the intracorporeal pressure continued to rise; once the perfusion pump was switched off, however, the pressure started to decrease slowly. In two experiments the saline infusion was continued after neurostimulation had been terminated to see if the peak pressure could be maintained without any further stimulation of the cavernous nerves: after about 2 min, the pressure abruptly dropped to baseline or slightly above (Fig. 1).

Four dogs underwent neurostimulation during saline infusion at each of the two rates. In three, the erection response was small at the lower rate (pressure rise above baseline, 0 to 38 cm H_2O), which is in agreement with our previous finding that an individual threshold infusion rate is necessary to achieve full erection (Lue *et al.*, 1983a) (Fig. 2). With the higher perfusion rate, the pressure response to neurostimulation was as described and full erection developed in each animal.

Discussion

Our results clearly show that venous outflow restriction takes place during erection and that it is necessary not only to induce full erection but also to maintain it.

In this animal model we were able to study the venous component exclusively during erection induced artificially by saline perfusion and neurostimulation.

Full erection was not achieved with saline perfusion alone, nor could the peak pressure response be maintained in any of the dogs with the flow rates of 0.9 and 1.9 ml/min. Once the flow rate was high enough to initiate a pressure rise in the corporeal tissue, the pressure stabilised at a certain point or,

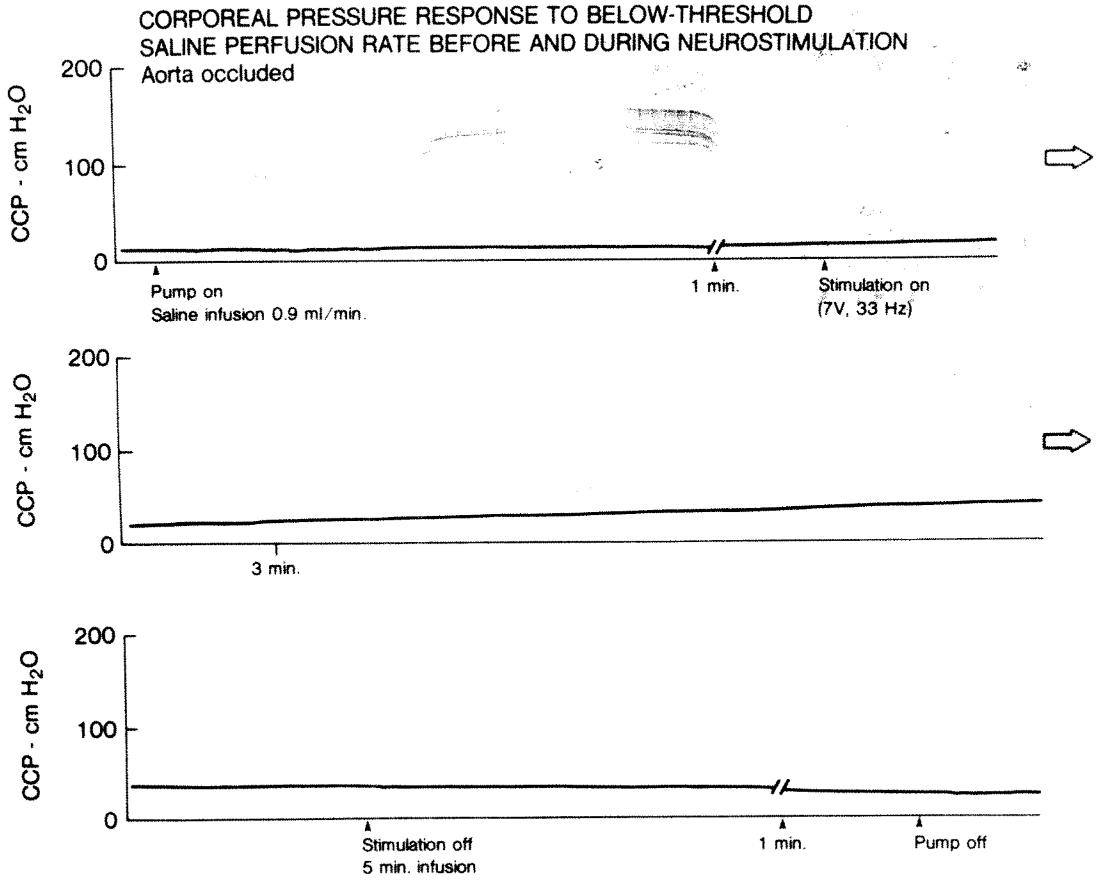


Fig. 2 Representative intracorporeal pressure response in one dog to perfusion of normal saline at a "below-threshold" rate (0.9 ml/min) before and during neurostimulation (aorta clamped). Note that even with neurostimulation (7 V, 33 Hz), it is impossible to achieve full erection because the perfusion rate is too low. (CCP = corpus cavernosum pressure).

if it rose above 50 cm H_2O, it dropped to or slightly above its baseline level. It is clear that the venous outflow resistance decreases at a certain pressure point to allow a rapid efflux of fluid from the penis, but the reason for this is as yet unknown. In the human studies of Newman and Reiss (1984), intracorporeal saline perfusion at 250 ml/min failed to induce full erection in some potent and impotent men, and one could speculate that the venous outflow capacity adapts to a higher artificial arterial inflow as long as no stimulant (*e.g.* drug [Juenemann *et al.*, 1985] or neurostimulation) is present to induce venous outlet restriction. Our results with neurostimulation during controlled saline perfusion show that an active venous occlusion must have taken place when the cavernous nerve was stimulated and no additional flow into the penis other than the perfusate was allowed.

Our understanding of the mechanism of venous occlusion is that active relaxation of the intracorporeal smooth muscle cells (*e.g.* by cavernous nerve stimulation) is the key contributing factor. The initial drop in corporeal pressure with neurostimulation indicates that active relaxation of the sinusoids takes place first, then 5 to 10 s later the pressure starts to rise. It seems logical that most of the venous occlusion during erection is caused by the active relaxation of the corporeal smooth muscle cells, although the occlusion is not complete. A minimal or "threshold" flow rate (Lue *et al.*, 1983a) is necessary to achieve full erection, even with neurostimulation. In three of the eight animals, full erection was not achieved during neurostimulation with the lower infusion rate (0.9 ml/min). The intracorporeal pressure rose to a certain point (to 18 and 38 cm H_2O in two [not at all in one]), where it stabilised until the stimulator was switched off or the flow rate was increased. This less than complete occlusive response supports our previous finding that an adequate intracorporeal blood supply is maintained during erection (Lue *et al.*, 1983a). At this plateau, the inflow equals the outflow, which happens in physiological erection where the effective corporeal perfusion pressure decreases to its minimum once full erection is achieved (Lue *et al.*, 1985). In our study, the inflow to achieve full erection during neurostimulation was maintained artificially, resulting in a constant pressure rise far above the systemic blood pressure.

One could suggest that the response to neurostimulation during saline perfusion with the aorta clamped was caused by additional arterial flow entering the corpora from the systemic circulation. To ensure that this had not occurred, both needles (for pressure recording and saline infusion) were opened to air at the conclusion of the experiment in two dogs, as recommended by Newman (personal communication). The saline had only a very slight bloody tinge.

We conclude that there is a definite reduction in venous capacity during erection and recommend evaluation of venous as well as arterial competence (Lue *et al.*, 1984, 1985) during the investigation of impotence.

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The Authors

K.-P. Juenemann, MD, Research Fellow in Urology.
J.-A. Luo, MD, Research Fellow in Urology.
T. F. Lue, MD, Assistant Professor of Urology.
E. A. Tanagho, MD, Professor and Chairman, Department of Urology.

Requests for reprints to: T. F. Lue, Department of Urology, University of California, San Francisco, CA 94143, USA.

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Radiation-induced Carcinoma of the Penis

A. D. WELLS and J. P. PRYOR

Department of Urology, King's College Hospital, London

Summary—Two patients with carcinoma of the penis were treated with interstitial radiation. They were cured of their disease for 17 and 21 years respectively and then developed radiation-induced tumours.

Carcinoma of the penis is often treated with irradiation. Local recurrence is unusual and the results obtained in Stage 1 and 2 disease are certainly comparable with those obtained by surgical excision (Jackson, 1966; Cabanas, 1977; Salaverria *et al.*, 1979). Many patients, particularly in the younger, sexually active groups, prefer radiation therapy to what many regard as mutilating surgery. Complications such as urethral stenosis, urethral fistula and radiation necrosis are well recognised, but the complication of a radiation-induced tumour following radiotherapy for carcinoma of the penis has not previously been described.

Case 1

W.P. was a 45-year-old male who presented with carcinoma of the penis in 1938 and was treated by circumcision and local implantation of radium needles around the tumour. The inguinal nodes were irradiated during the post-operative period, although there had been no definite evidence of metastatic disease. The patient's response to treatment was excellent and there was no evidence of recurrent disease. Twenty-one years later he was seen again on account of a bleeding ulcer of the glans penis. This had the appearance of a localised carcinoma of the penis and there was no enlargement of the inguinal nodes. Biopsy confirmed the presence of a poorly differentiated squamous cell carcinoma and partial amputation of the penis was performed. The post-operative course was uneventful and there was no sign of recurrent disease. Four years later the patient developed a carcinoma of the stomach which was treated by partial gastrectomy. He died 3 years later of carcinoma of the stomach but there had been no evidence of any recurrence of the disease of his penis or inguinal lymph nodes up to the time of his death.

Case 2

F.B. was a 52-year-old male who presented in 1959 with a 6-week history of penile discomfort and swelling. Examination revealed phimosis with a suspicious indurated area at the tip of the glans penis. He was circumcised and the area biopsied. Histology confirmed the presence of a well differentiated squamous cell carcinoma of the penis and he was treated by the insertion of seven radioactive gold grains around the tumour. The post-operative course was uneventful and he attended for regular follow-up examinations. In 1972 he developed a meatal stricture and meatomy was performed. There was no evidence of any tumour at this stage, but in 1977 he complained of soreness of the glans penis and was found to have a small ulcer in the coronal sulcus extending on to the dorsal surface of the glans penis (Fig.). This ulcer was not directly related to the ventrally placed gold grains. Biopsy of this lesion confirmed the presence of a well differentiated squamous cell carcinoma of similar appearance to that seen in 1959. He was treated by partial amputation of the penis and remains well with no evidence of recurrent or metastatic disease.

Discussion

Radiation is a well recognised carcinogen and since

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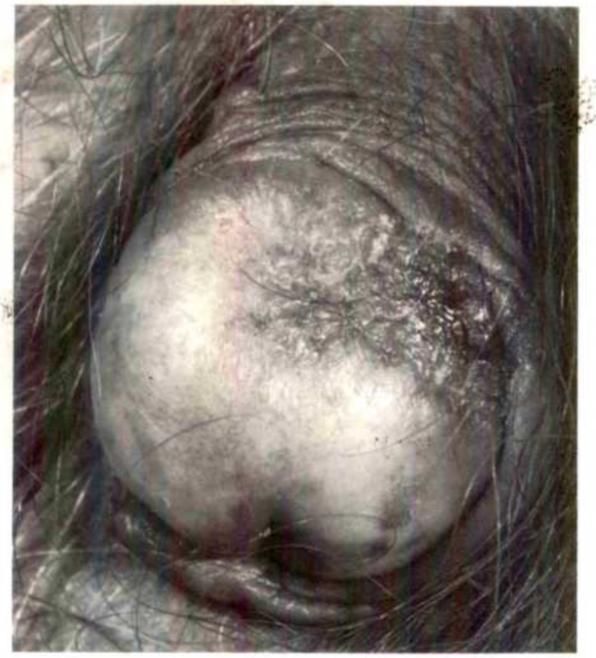

Fig. Radiation-induced tumour in coronal sulcus extending on to dorsal surface of glans penis.

the first reported case of radiation-induced tumour in 1902 (a prickle cell carcinoma of the skin) (Frieben, 1902) many others have been recorded. When a malignant tumour develops following whole body irradiation (Beebe *et al.*, 1978), after irradiation for benign conditions (Court Brown and Doll, 1965; Favus *et al.*, 1976; Modan *et al.*, 1977; Boice *et al.*, 1979), or it develops in tissue other than that originally irradiated (Li *et al.*, 1975), then it may be possible to postulate radiation as the carcinogenic agent. A problem arises, however, in differentiating between a radiation-induced tumour and local recurrence when a tumour similar to the one originally irradiated develops within the field of treatment. Points in favour of a radiation-induced tumour include a long latent period between treatment and induction (Pizzarello *et al.*, 1984), the induced tumour may appear at the periphery of the treatment field, if the centre of the field has been sterilised by the irradiation (Pizzarello *et al.*, 1984), and the histology of the tumour may show rather bizarre forms compared with the original lesion.

In the two reported cases the most striking feature was the length of the latent period between the initial radiation treatment and subsequent appearance of the tumour, 21 years in Case 1 and 17 in Case 2. The exact site of the second tumour in relation to the original treatment field has been difficult to determine from the first patient's notes, but for Case 2 it appears that the second tumour developed at the periphery of the irradiation field. We feel that in both cases a diagnosis of local recurrence is unlikely and one of radiation-induced carcinoma probable. The existence of this complication emphasises the need for careful evaluation of each patient before deciding upon irradiation therapy as the optimum form of treatment. This becomes particularly relevant in younger patients who, if cured of their disease, may well have a life expectancy in excess of a further 20 years.

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The Authors

A. D. Wells, FRCS, Urology Registrar.
J. P. Pryor, MS, FRCS, Consultant Urologist.

Requests for reprints to: A. D. Wells, Department of Urology, King's College Hospital, Denmark Hill, London SE5 9RS.

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A Computerised Urodynamic System

B. G. BEST, S. R. JOHNSTON, J. A. KENNEDY and W. G. G. LOUGHRIDGE

Department of Urology, Belfast City Hospital, Belfast

Summary—A new urodynamic investigation system, based on a microprocessor, is described. The design principles, versatility and advantages of the equipment are discussed. It is concluded that this system offers significant benefits to the urodynamic unit for both routine and research work.

Our understanding of lower urinary tract function has advanced rapidly over the past decade. New concepts appear in the literature almost monthly and increasingly complex analyses are required. In the light of these developments, previous cases often have to be reviewed, and this requires an efficient file system. We felt that the stage had been reached for the computerisation of urodynamics to facilitate data analysis and file handling. Our initial thought, to interface a computer to an existing system, seemed unnecessarily complex as it would involve a mixture of analogue and digital signals for much of the procedure. We therefore designed a new urodynamic system using a powerful microcomputer, with integral VDU monitor and dual disk drives, linked to a dot matrix printer.

Materials and Methods

The microcomputer is an ACT Sirius 1, with its 800 × 400 resolution monitor and dual disk drives (which use 5.25 inch floppy disks). The printer is an Epson MX80 F/T III.

The Sirius 1 was chosen for its 512K RAM memory, needed for storage and analysis of the large amount of incoming data, and its high resolution monitor which permits fine detail to be displayed. The operating program disk remains in one drive while data is stored on to, or read from, disks in the other drive.

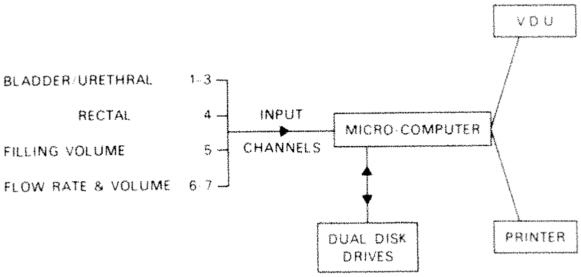

Fig. 1

The dot matrix printer is used to draw the graphics and print the results.

Programs are written in Forth and Machine Code computer languages, using the CP/M operating system.

The bladder and urethral pressures are measured by Gaeltec catheter-mounted transducers which, owing to their very fast response times, enable short duration events to be recorded. The rectal pressure is measured by an external Gaeltec transducer attached to the usual fluid filled line. A weight transducer records filling volume (Fig. 1). The flow meter is unique and will be discussed in detail later.

The input signals, which are in analogue form, are filtered to an upper range of 30 Hz depending on the frequency response of the measuring equipment. They pass to an analogue-digital converter which samples the waveform at 8 to 64 times per second and expresses the results in a computer readable form (Asbury, 1983). The sampling rate can be altered at will to the optimum for each signal without interrupting the recording. The digital

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Based on a Poster Demonstration at the 41st Annual Meeting of the British Association of Urological Surgeons in Eastbourne, July 1985

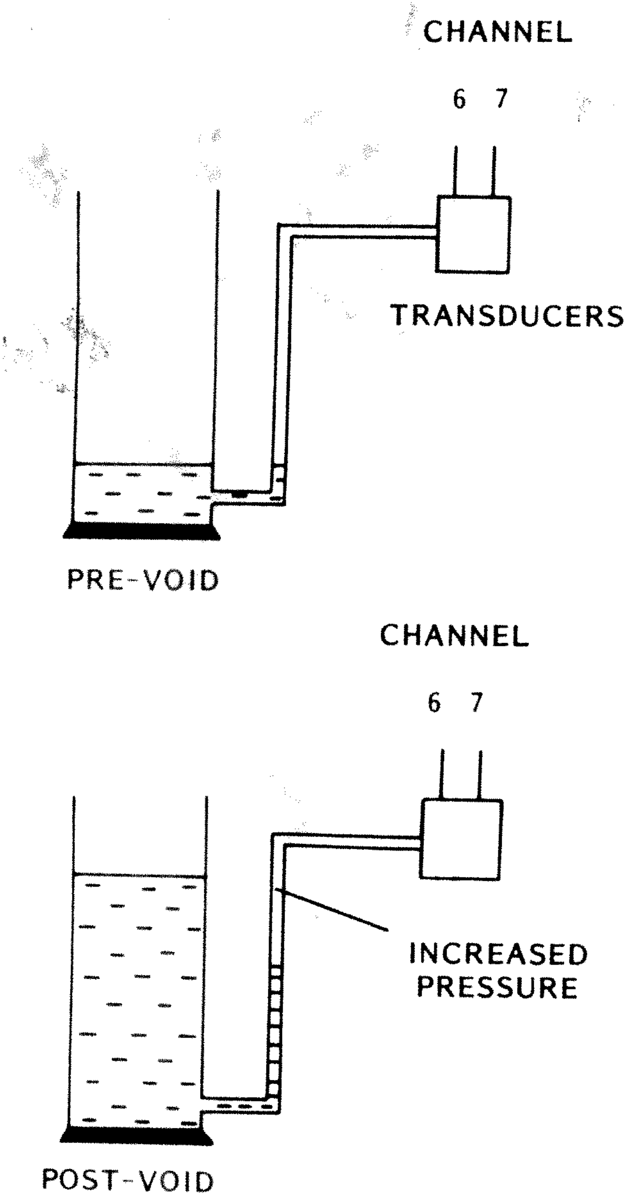


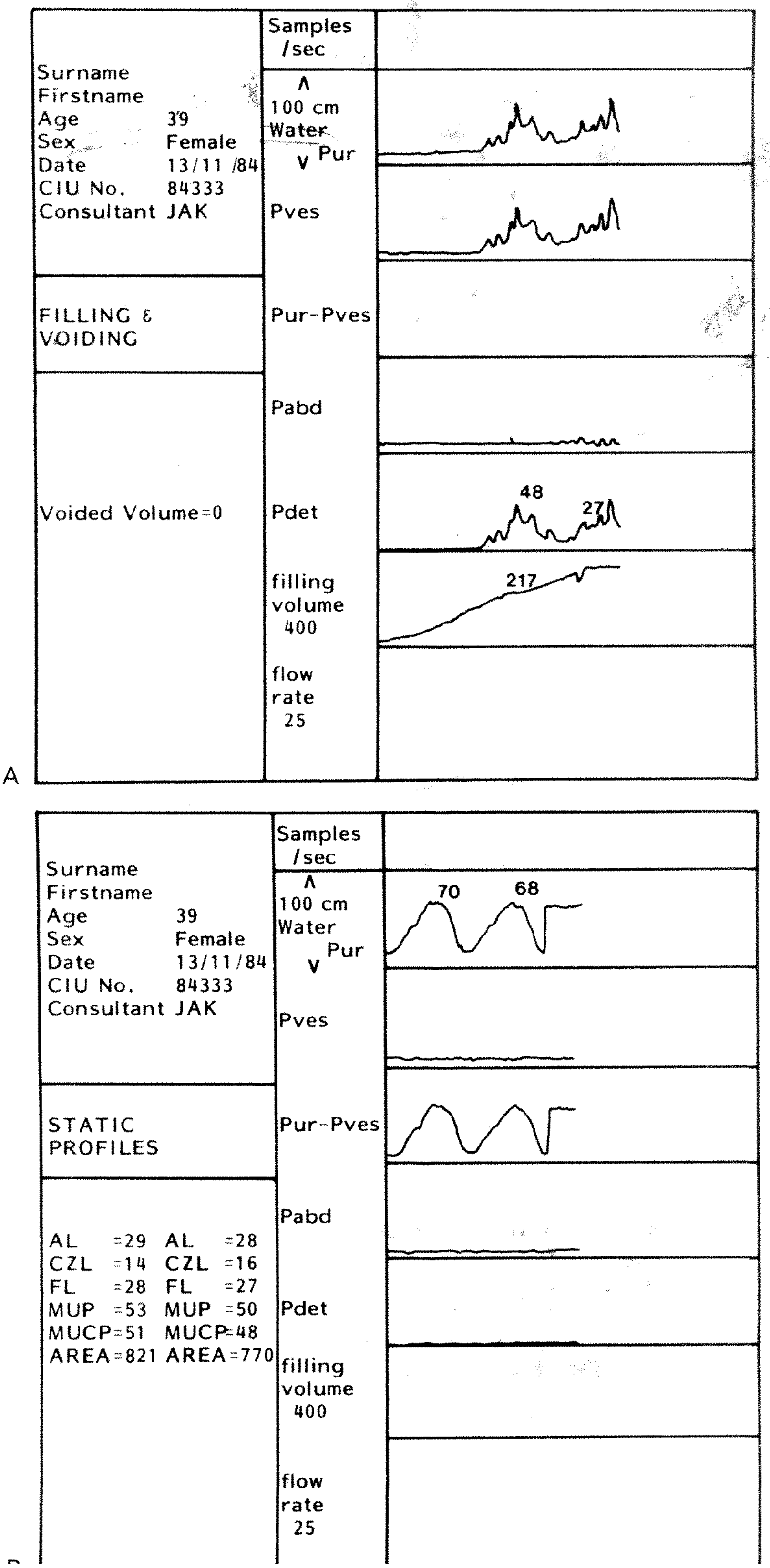
Fig. 2 Flow meter.

signals are stored in the microcomputer memory and are used to produce a "real-time" visual display. On completion of the urodynamic assessment, the data are reviewed and analysed, as desired, by the computer. A printout (A4 size) of the curves and their analyses is then obtained. The data can be directly stored on computer disks, permitting future additional analysis.

The flow meter (Fig. 2) is a one-litre plastic jug with a fine bore side arm, connected to a pressure transducer. A removable baffle eliminates turbulence. As the level of urine rises during micturition, the air in the side arm is compressed. The rate of change and total rise in pressure are computed into flow rate and volume. The recording automatically begins with the first change in pressure. A memory buffer holds data for 10 s and the computer reads the preceding 10 s after initiation. This ensures that the true start of micturition is included. The calibration allows for rates of up to 50 ml/s and volumes of up to 1000 ml. The response and oscillation times have been tested against known constant flows of square wave pattern. The equipment is accurate to within 1% for both rate and volume. The flow meter is also available as a separate portable unit, using a battery powered Epson HX 20 computer.

The urodynamic routines are stored on floppy disks and include the operating and mathematical instructions for the various types of analysis.

Our standard program consists of uroflowmetry, filling and voiding cystometry, and urethral pressure profilometry. At present we do not use EMG recording. However, if required, the EMG signal may be fed into channel 3 after appropriate program modification. Analytical parameters may be assessed at any part or parts of the traces. These parameters include values of pressure and volume, flow rates, areas under curves, slope gradients and urethral lengths. Automatic selection of maximum values is a useful feature. The appropriate program is loaded at the start of the urodynamic session. Patient details are typed in on the computer keyboard. The actual clinical procedure is the same as for other systems. Briefly, the patient is asked to attend the clinic with a full bladder and an initial flow rate is obtained. The patient then lies on the examination couch and the rectal line (5 Fg) is inserted. The filling catheter (10 Fg) and the double transducer catheter (6 Fg) are passed simultaneously under urethral anaesthesia. Any residual urine is noted. The proximal transducer is placed at the distal sphincter while the distal transducer lies free within the bladder; the catheter is kept in position by attaching it to the arm of the catheter puller. Filling cystometry is performed and the filling catheter is then removed. When the patient is moving from the supine to standing position, the catheter is held in place by the operator or nurse. Voiding cystometry is performed. The urethral profile is obtained using an electric motor catheter puller to ensure a constant and accurate rate of withdrawal. Events are marked on the screen as they occur, *e.g.* desire to void, using the appropriate key on the keyboard.



A

Surname
Firstname
Age 39
Sex Female
Date 13/11 /84
CIU No. 84333
Consultant JAK

FILLING & VOIDING

Voided Volume=0

Surname
Firstname
Age 39
Sex Female
Date 13/11/84
CIU No. 84333
Consultant JAK

STATIC PROFILES

AL =29 AL =28
CZL =14 CZL =16
FL =28 FL =27
MUP =53 MUP =50
MUCP=51 MUCP=48
AREA=821 AREA=770

Fig. 3 A. Filling and voiding profile of patient with primary detrusor instability. B. Static urethral profile of patient with primary detrusor instability.

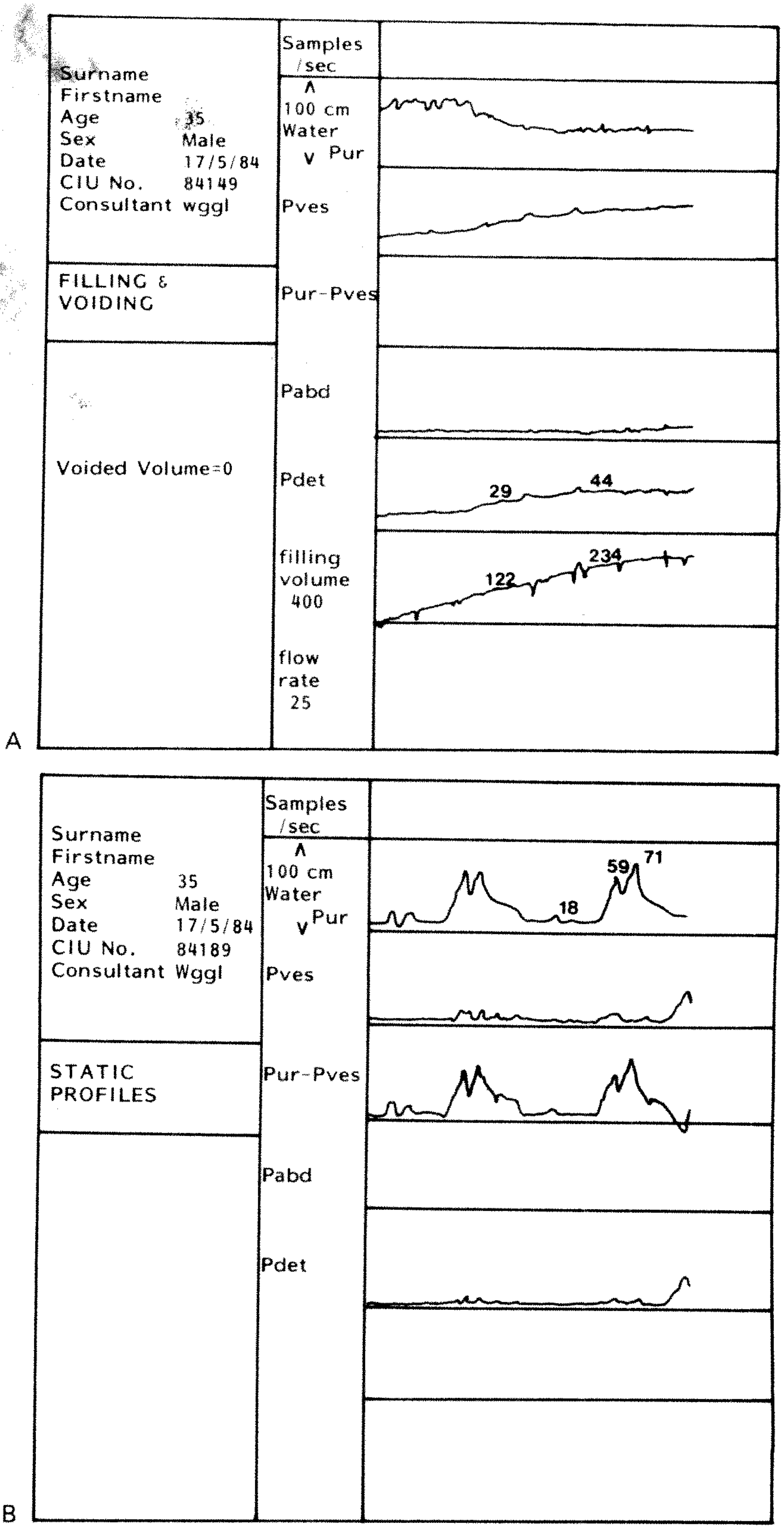


Fig. 4 A. Filling and voiding profile of patient with outlet obstruction. B. Static urethral profile of patient with outlet obstruction.

We use a double transducer catheter routinely, though single and triple transducer catheters are used in some of the research studies. The double transducers allow synchronous measurement of bladder and urethral pressures. This is especially valuable in urethral profilometry as it allows detrusor activity to be monitored during the profile.

Results

We have used this system since August 1982. Apart from a few initial design modifications and some alterations to the routine program, we have not encountered any disadvantages. Many advantages have become apparent as experience has been gained. Ease of use has resulted in shorter procedure times, allowing 66% more patients to be studied in a similar preceding period. The compactness of the unit and the simplicity of the flow meter, with automatic start, result in a more relaxed patient. Many patients, in fact, pass the time watching the screen; detrusor instability can then easily be explained to the patient and a biofeedback treatment programme started, if appropriate. The nursing staff have found the flow meter very easy to clean quickly and to set up for the next patient. Immediate access to patient records stored on disk has been helpful at follow-up clinics.

Two examples of urodynamic studies are shown. Figure 3 shows the filling cystometric and static urethral profile traces of a 39-year-old female suffering from primary detrusor instability. Figure 4 shows the urodynamic findings in a 35-year-old man with symptoms of outlet obstruction. He was unable to void at the clinic. Filling cystometry shows a detrusor pressure of 44 cm of water at a volume of 295 ml. Urethral profilometry shows a double (pre-sphincteric) peak suggestive of bladder neck hypertrophy. This was confirmed at cysto-urethroscopy.

Discussion

A major benefit of this system is the ease with which any type of analysis may be obtained, no matter how complex. When new concepts demand new mathematical formulae, the program may be altered accordingly or a separate one written. The system is "user friendly", *i.e.* no computer knowledge is required by the operator. However, if program writing is to be undertaken, considerable expertise is needed. If this is not available in the hospital/university, Gaeltec Research Ltd will supply programs, from their program library, with the system and they will write programs to meet specific requirements.

An additional benefit is that it is far more than just a urodynamic system. It is still a powerful microcomputer and can be used for several different functions in the urological unit such as word processing, data files, statistics. Many independent commercial computer programs are immediately compatible with the urodynamic records because of their common program language and operating systems.

The cost of the complete system is similar to that of conventional 6-channel machines. The running costs are low as fanfold computer paper is considerably cheaper than flow chart paper.

In conclusion, the inherent versatility and capacity of this system offers significant benefits for routine and research urodynamic studies. The urological unit also benefits from its microcomputer functions.

Acknowledgements

We thank Donald MacLachlan, BSc, ARCS, of Gaeltec Research Ltd, Dingwall, Scotland, who undertook the design and production of the system.

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The Authors

B. G. Best, FRCS, Senior Surgical Registrar.
S. R. Johnston, FRCS, Consultant Urological Surgeon.
J. A. Kennedy, MCh, FRCS, Consultant Urological Surgeon.
W. G. G. Loughridge, MA, MD, FRCS, Consultant Urological Surgeon.

Requests for reprints to: S. R. Johnston, Department of Urology, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB.

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Case Reports

Massive Haematuria due to an Ilio-ureteric Fistula

J. D. BEARD, P. G. SOMERVILLE, J. P. WARD, K. C. PERRY and H. DEXTER, *Departments of Surgery, Royal Sussex County Hospital, Brighton and Eastbourne General Hospital, Eastbourne*

Case Report

A 74-year-old man presented with sudden onset of massive haematuria 3 months after an uneventful TURP for benign prostatic hypertrophy. Twelve years previously an aorto-bi-iliac endarterectomy, with application of dacron patch grafts, had been performed for claudication. Physical examination was unremarkable, a provisional diagnosis of prostatic bleeding was made and blood transfusion commenced.

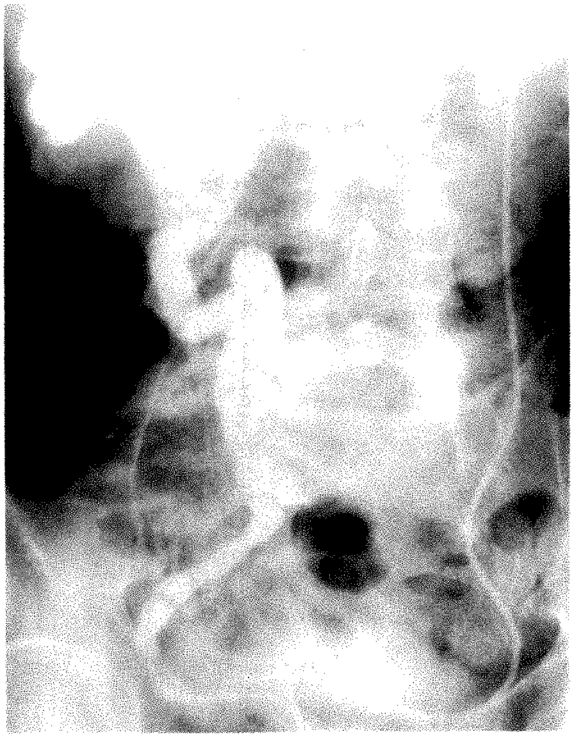

Fig. Retrograde uretero-pyelogram demonstrating a right-sided hydronephrosis and hydro-ureter down to the pelvic brim with a blind track passing medially at this point.

IVU showed delayed excretion on the right side with hydronephrosis. Cystoscopy revealed a normal urethra, prostatic remnant and bladder. Retrograde uretero-pyelography showed a right-sided hydronephrosis and hydro-ureter down to the pelvic brim with a blind track passing medially at this point (Fig.). Ultrasonography demonstrated dilatation of the aortic bifurcation and common iliac arteries.

Laparotomy revealed an aneurysm of the aortic bifurcation and right common iliac artery. The dacron patch was densely adherent to the right ureter with erosion into the ureter at the suture line. A woven dacron aorto-bi-iliac graft was inserted, the adherent portion of the ureter excised and the ureter reanastomosed over a silastic double-J stent anterior to the graft. The ureter and graft were separated by suturing the aneurysm sac over the graft and wrapping the ureter in omentum.

The post-operative course was uneventful, the stent being removed at cystoscopy 3 weeks later. IVU at 6 months showed no obstruction.

Comment

Ilio-ureteric fistulae are very uncommon and we can find no previous record of one following endarterectomy, although a primary ilio-ureteric fistula due to an iliac artery aneurysm has been reported (Rennick *et al.*, 1976). The main cause of arterial graft erosion into the gastrointestinal tract is thought to be inadequate coverage of the graft, particularly at the site of anastomoses (Kleinman *et al.*, 1979). This probably applies equally to the renal tract and to avoid this complication the graft or patch should be separated from the ureter by interposition of soft tissues, including the aneurysm sac, especially if there is an anastomosis or suture line at this level. Positioning the ureter anteriorly has been recommended in the past to avoid the possibility of ureteric obstruction. This presumably applies to fistula formation as well, although the advantage of this procedure has been questioned (Thomas *et al.*, 1983).

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Requests for reprints to: J. D. Beard, Vascular Studies Unit, Level 7, Bristol Royal Infirmary, Bristol BS2 8HW.

Primary Penile Urethral Carcinoma

S. A. MAHMOOD and J. A. THOMAS, *Department of Pathology, St John's Medical College, Bangalore, India*

Levine (1980) stated that only about 400 patients with this rare neoplasm have been reported in the last 151 years.

Case Report

A 35-year-old married farmer, with a history of venereal disease, passed urine through many fistulae at the bulb of the swollen penis and scrotum. The condition had started as a local nodule 5 months earlier. Many fistulae were observed on the ventral aspect of the penis, proximal to the scrotum. The edges of these openings were everted, friable, and indurated and the largest measured 5 × 2.5 cm (Fig. 1). Both the superficial and deep inguinal nodes were tender, mobile and soft-to-firm in consistency.

Initial biopsy from the fistulous area showed a squamous cell carcinoma; a peno-scrotal excision was made 23 days after admission (Fig. 2). Both testes were reimplanted in the thighs. Nodular neoplastic deposits were observed on the left spermatic cord. The inguinal lymph nodes on biopsy showed no evidence of metastasis. The patient's condition improved initially but on the 44th post-operative day a metastatic nodule was found associated with the left testis and on the 50th post-operative day the patient's condition rapidly deteriorated, with haemorrhage at the site of operation. He was transferred to a cancer hospital and was lost to follow-up.

Comment

This patient's presentation and subsequent progress reflect the features peculiar to this rare neoplasm, emphasised by Kaplan *et al.* (1967). These features include age, history of venereal disease, clinical presentation and bulbo-membranous urethral involvement with slow insidious progression and local spread. The rarity of penile urethral carcinoma is interesting in this geographical area where urinary bladder cancer and penile cancers are more common, their respective ratios being 1:110:131 (1966-1984).

Acknowledgement

The authors acknowledge the secretarial help of Mrs S. Varalakshmi.

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Requests for reprints to: J. A. Thomas, Department of Pathology, St John's Medical College, Sarjapur Road, Bangalore 56 00 34, India.

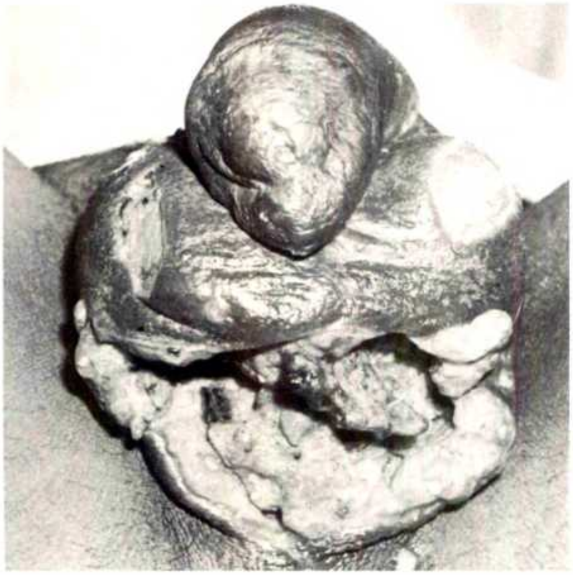

Fig. 1 Note the fistulous openings at the penile bulb proximal to the scrotum.

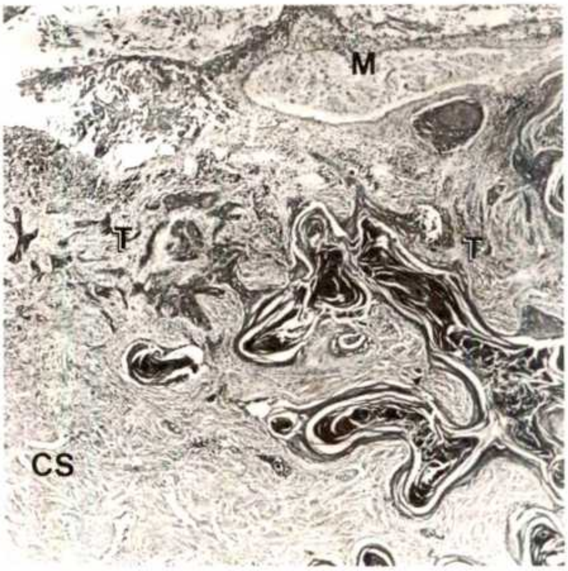

Fig. 2 A portion of the ulcerated urethra (M) with a squamous cell carcinoma (T) and corpus spongiosum (CS). (H and E × 25).

Intrarenal Arteriovenous Fistula: a Cause of Reversible Hypertension

A. A. SIDI, P. JONAS, T. ROSENTHAL and M. MANY,
Departments of Urology and Internal Medicine, Chaim Sheba Medical Center, Tel-Hashomer and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Case Report

A 41-year-old healthy male was found on a routine check-up to have elevated blood pressure (180/120 sitting and standing) with a pulse rate of 120/min. Electrocardiography showed left ventricular strain.

Intravenous urography (Fig. 1) showed a sharply outlined mass, 3 cm in diameter, compressing and deforming the right renal pelvis and the upper and middle calices. Delayed films demonstrated an accumulation of contrast material in the mass. Ultrasonography showed the characteristic features of a fluid-containing mass. Transfemoral percutaneous angiography showed two right renal arteries and an intrarenal aneurysmatic malformation. On selective angiography (Fig. 2) an arteriovenous fistula consisting of a large aneurysmatic dilatation of the lower renal artery draining into the main vein via a small vessel was demonstrated. The arterial supply to the upper two-thirds of the kidney was normal. Bilateral renal vein catheterisation and renin studies, before and after provocation by converting enzyme inhibitor (SQ 20881), showed no lateralisation.

Beta-blocker medication controlled the blood pressure for 4 months. He then developed severe incapacitating headaches and a further rise in blood pressure. Exploration of the right kidney through a flank incision revealed two equal-sized renal arteries originating from the aorta and one single main renal vein. On further dissection a small pulsating blood vessel draining into the main renal vein was found (Fig. 2: arrow). On clamping the lower renal artery the pulsation in the small vessel ceased and the lower third of the kidney turned ischaemic. The lower renal artery and the pulsating vessel were ligated and divided and a lower pole nephrectomy was performed.

The patient had an uneventful post-operative course. His blood pressure returned to normal and remained normal without medication during a 6-month follow-up period.

Comment

Most renal arteriovenous fistulas are secondary to trauma, mainly percutaneous renal biopsy, rupture of aneurysms or renal carcinoma, but some are primary and congenital. Haematuria, high output cardiac failure and hypertension are the characteristic clinical features. Hypertension occurring in patients who developed a renal arteriovenous fistula following renal biopsy has been cured by nephrectomy (Bass and Lipper, 1975), partial nephrectomy (Riba and Simon, 1967) or arterial occlusion (Wallace *et al.*, 1978). Renal vein studies in our patient showed no increased renin release from the right kidney but the increased blood flow could well have masked this.

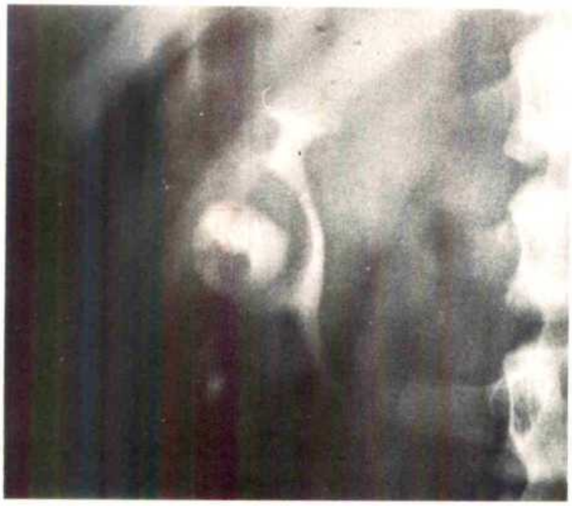

Fig. 1 Intravenous urography: right kidney—peripelvic mass filled with dye.

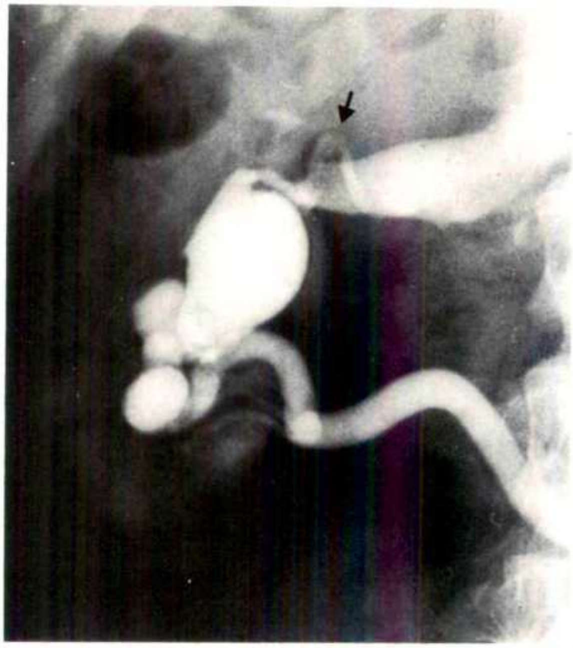

Fig. 2 Angiography: selective injection into right inferior renal artery, large aneurysmal dilatation draining via small vessel (arrow) into the main renal vein.

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Requests for reprints to: A. A. Sidi, Department of Urology
Chaim Sheba Medical Center, Tel-Hashomer, Israel.

Wegener's Granulomatosis with Infiltration of the Prostate

I. T. SÖZER, *Department of Urology, Haydarpasa Numune Hospital, Istanbul, Turkey*

Wegener's granulomatosis is characterised by necrotising granulomatous lesions of the respiratory system, by generalised necrotising vasculitis and by glomerulonephritis.

Case Report

A 53-year-old male was admitted with a 2-year history of nocturia and a slowing stream. He also had a history of chronic upper respiratory infection, loss of weight and a deformity of the nose.

A suprapubic prostatectomy was performed and histological examination of the prostate revealed scattered necrotising granulomatous lesions and vasculitis of the small vessels. He made a good recovery but was readmitted 6 months later because of slowing urination and a purulent rhinitis. He had an almost complete nasal obstruction with a pronounced saddle deformity. The nasal cavity was filled with pus and granulomatous tissue and the nasal septum was almost entirely destroyed. Rectal examination disclosed a mobile, tender, boggy, nonnodular mass in the prostatic area. He was anaemic and had a slight leucocytosis and a BUN of 92 mg/100 ml.

At cystoscopy the prostatic urethra was occupied by greyish necrotic material, a biopsy of which was interpreted as necrotising prostatitis. He was discharged with an indwelling catheter and died 25 days later.

Comment

Involvement of the prostate in Wegener's granulomatosis occurs in 7.4% of cases and 11 cases have been reported in the literature. In four of these the prostatic symptoms predominated (Yalowitz *et al.*, 1966).

The diagnosis should be suspected when upper and lower respiratory disease occurs together with evidence of renal involvement and can be confirmed by the histopathological demonstration of necrotising granulomatous vasculitis in the appropriate tissues. The renal component usually determines the course and ultimate outcome of generalised Wegener's granulomatosis (Fauci, 1979). Other parts of the urogenital system, including the prostate, the seminal vesicles and the testis, can be affected (Berman *et al.*, 1963). Cytotoxic agents are the treatment of choice and cyclophosphamide seems the most effective.

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Requests for reprints to: I. T. Sözer, Department of Urology,
Haydarpasa Numune Hospital, Istanbul, Turkey.

Inverted Multifocal Papilloma of the Bladder

F. ARAGONA, V. SERRETTA and A. MARIANI, *Urology Service, Institute of General Surgery, and Department of Pathology, University of Pisa, Pisa, Italy*

The seventh reported case of multifocal inverted papilloma of the bladder is presented. It is essential to distinguish it from low grade transitional cell carcinoma. Although the correct treatment is conservative, careful follow-up is necessary.

Inverted papilloma is a rare polypoid lesion of the urinary tract first described by Potts and Hirst

(1963). More than 110 cases have been reported since then (Caro and Tessler, 1978) and over 85% occur in the region of the trigone, bladder neck or posterior urethra. It is generally considered benign, although two cases of malignant transformation have been reported by Uyama *et al.* (1980) and Whiterel (1982).

Case Report

A 74-year-old male was observed in February 1983 with a 1-day history of gross haematuria and symptoms of lower urinary tract infection. His past history was unremarkable. IVU showed normal kidneys and ureters. Outpatient cystoscopy revealed two small papillomas, one at the trigone and the other on the right lateral wall; both were fulgurated. Biopsy showed the pathological changes of inverted papilloma (Fig.). One month later cystoscopy revealed a hyperaemic, oedematous area just behind the right ureteric meatus; this was treated by fulguration. No evidence of recurrence was found at follow-up cystoscopy in April 1983. Bladder mapping, transrectal echography and a CAT scan in May 1983 were unremarkable.

Comment

The histogenesis of inverted papilloma of the bladder remains unclear but many authors attribute it to irritating processes or hyperplasia of von Brunn's glands (Cummings, 1974; Matz *et al.*, 1974).

According to previous reports, this lesion is benign and recurrence is rare (De Meester *et al.*, 1975; Cameron and Lupton, 1976). A few cases of malignant transformation have been reported (Uyama *et al.*, 1980; Whiterel, 1982) but the possibility of the coexistence of two different tumours must be considered. Endoscopic examination provides no criteria leading to the diagnosis of inverted papilloma and histological investigation is essential. Microscopic examination of inverted papilloma shows a surface covered by normal urothelium. Epithelial cords of cells indistinguishable from normal elements extend down into the connective tissue, at times with a small cyst in their centre containing PAS positive material. Iwata *et al.* (1982) observed secretory granules in the apical portion of these cells; these granules are not present in normal and neoplastic cells and demonstrate a particular differentiation of inverted papilloma cells. These findings suggest that inverted papilloma of the bladder is a separate pathological entity and should not be confused with other bladder lesions. We believe that correct microscopic diagnosis is essential to distinguish between inverted papilloma and low grade transitional cell carcinoma. This is the most important criterion for correct management.

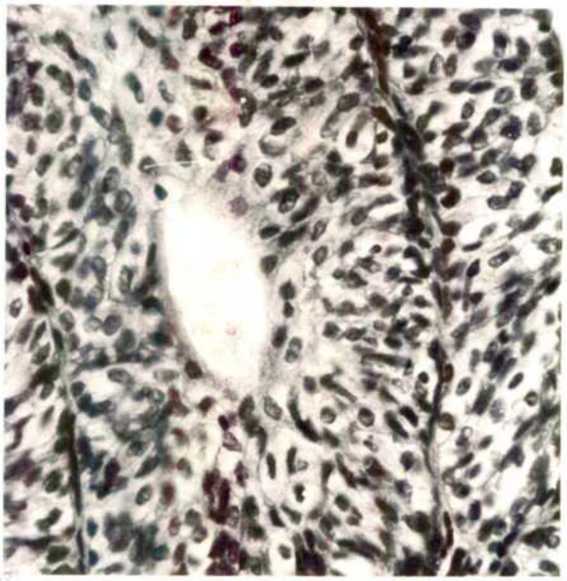

Fig. Characteristic formation of tumour cell with "palisading" of cuboidal outer layer of cells and cyst formation. (H and E × 1000).

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Requests for reprints to: F. Aragona, Clinica Chirurgica Generale, Via Roma 57, 56100 Pisa, Italy.

Colonic Infarction Following Ethanol Embolisation of the Kidney

P. D. SUTHERLAND, P. R. HOWARD and V. R. MARSHALL, *Department of Urology, Flinders Medical Centre, Bedford Park, Australia*

Case Report

A 78-year-old male with a T4 transitional cell carcinoma of the bladder which had not responded to palliative radiotherapy presented with severe right loin pain. An intravenous urogram demonstrated obstruction of the right ureter at the vesicoureteric junction by the tumour mass. Regular intramuscular narcotic failed to alleviate the pain and after a week, nephrectomy was considered in order to relieve the pain. However, in view of the advanced nature of the malignancy it was thought that embolisation of the kidney would afford less morbidity with the same result.

Ethanol was chosen as the embolising agent. Selective catheterisation of the right renal artery was performed in the supine position, using a Cobra 2 catheter which was positioned at least 2 cm into the artery. The hydronephrotic right kidney was fed by a single artery and had a normal arterial tree. Contrast demonstrated good position of the catheter and no reflux on injection at the planned embolisation speed; 15 ml of ethanol were injected at a rate of 1 ml/s under constant screening to avoid unseen catheter dislodgement. Excellent infarction was obtained.

Within a few hours the patient developed a fever, abdominal distension and a tender mass in the left iliac fossa. At laparotomy the left colon from mid-transverse to rectum was infarcted despite an intact and pulsatile inferior mesenteric artery. Proctocolectomy was performed and an end colostomy created. The patient's right loin pain, the indication for infarction, settled satisfactorily.

Comment

Since the initial successful reports of the use of ethanol, Cox *et al.* (1982) have reported two cases of concomitant colonic infarction identical to that observed in this patient. We feel that ethanol, which presumably refluxed into the aorta, failed to mix because of laminar aortic blood flow and passed undiluted into the first anterior blood vessel, the inferior mesenteric artery.

All of the previous reports of ethanol infarction have been in normal laboratory animal kidneys or hypovascular tumours. Our patient had a tense obstructed kidney and perhaps reduced renal blood flow could have increased the probability of ethanol escape, but the speed of injection and volume of ethanol used were half of that recommended by Ellman *et al.* (1981), who claimed that a major advantage of the ethanol technique was a low risk of accidental embolisation. Clearly this is incorrect if our case, plus those reported by Cox *et al.* (1982) and Mulligan and Espinosa (1983), are considered.

The technique needs further evaluation with regard to speed of injection, total dose and the type of catheter used. A balloon catheter to occlude the renal artery to avoid the escape of ethanol during injection could be considered.

It would seem that unless the reflux of ethanol can be prevented easily, the possibility of colonic infarction must counteract any benefit the technique has over other established methods of renal infarction.

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Requests for reprints to: V. R. Marshall, Department of Urology, Flinders Medical Centre, Bedford Park, Australia 5042.

Left Hydronephrosis due to Retroperitoneal Barytoma

E. PROCA, *Department of Urology, Fundeni Hospital, Bucharest, Romania*

Case Report

A 54-year-old male was admitted with left flank pain. Two months previously, rectosigmoidoscopy and barium enema had been performed and this was followed by excruciating abdominal pain due to subperitoneal rectal perforation and extravasation of the barium into the retroperitoneal space. The abdomen was opened and a left lateral sigmoid colostomy was performed. An attempt to drain the extravasated barium through a retroanal incision and blunt dissection of the presacral space failed and was followed by a perineal fistula and purulent discharge.

On admission to this department, proctoscopy revealed low rectal perforation and a presacral cavity

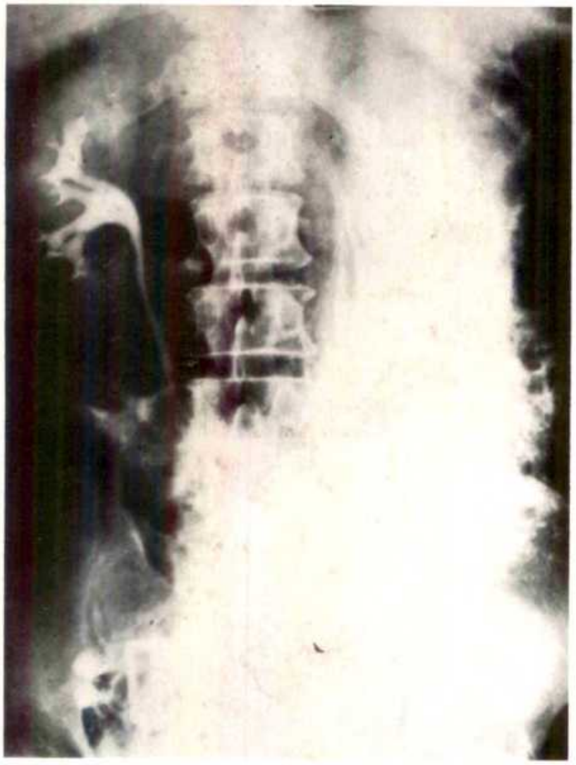

Fig. 1 Pre-operative IVU of patient with retroperitoneal barytoma.

with irregular fibrotic walls. Biopsy for tumour remained negative. Colonic fibroscopy through the stoma was also negative. On plain abdominal film the retroperitoneal space and a great part of the retroperitoneum, mainly on the left side, were densely opaque because of the extravasated barium (Fig. 1). IVU showed moderate left ureterohydronephrosis. Computed tomography confirmed retroperitoneal barium extravasation and dilatation of the left urinary tract (Fig. 2A).

Surgical exploration was undertaken to relieve the renal pain and ureteric compression. The retroperitoneal space was entered through a left Fey's abdominal incision. The barytoma presented as a whitish fibrotic mass, involving the retroperitoneal space and extending upwards around the aorta and left ureter. The renal pedicle was free of fibrosis and the renal pelvis greatly distended. The left ureter was dissected free with difficulty and mobilised down to the juxtavesical segment, where dissection proved to be impossible. Owing to the extensive thickening of the posterior peritoneum and the presence of the cutaneous sigmoid stoma, neither intraperitoneal ureteric transposition nor omental wrapping was attempted.

The patient had an uneventful post-operative course. The renal pain quickly subsided and he remained symptom-free for the following 6 months. IVU and CT scan demonstrated regression of the left hydronephrosis (Fig. 2B).

Comment

This is a rare complication and Vandendris and Giannakopoulos (1981) added the seventh reported case to the literature. Rectal perforation was facilitated in this case by the previous rectal instrumentation and by the use of a long rigid rectal cannula. The emergency left colostomy proved to be life-saving and is recommended for similar accidents.

We felt that surgical mobilisation of the obstructed ureter was preferable to prolonged ureteric catheterisation and steroid therapy. However, these alternative conservative measures may be necessary either as temporary treatment or if there are contraindications to operation.

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Requests for reprints to: E. Proca, Department of Urology, Fundeni Hospital, Bucharest, Romania.

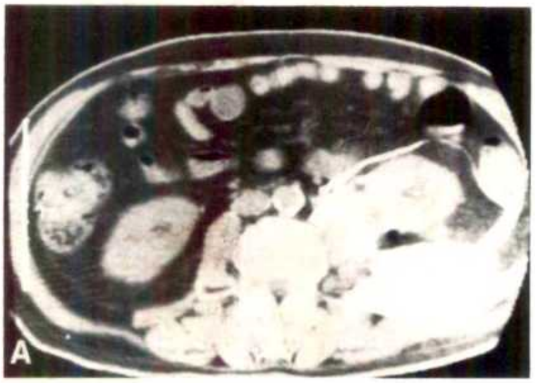

Fig. 2A Pre-operative CT scan.

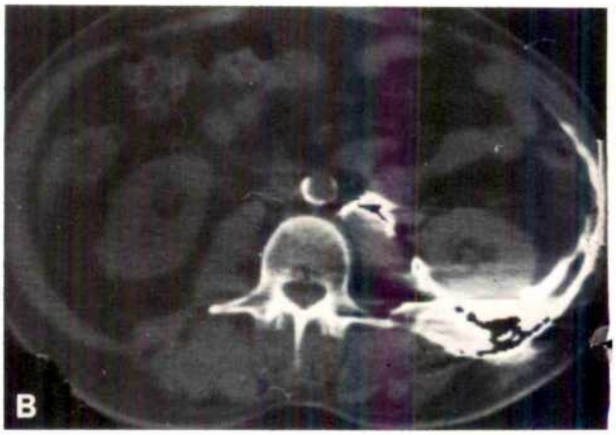

Fig. 2B Post-operative CT scan.

Renal Carcinoma Presenting with Peripheral Arterial Embolisation

G. J. C. M. NIESSEN and H. VAN URK, *Department of Surgery, University Hospital, Rotterdam, The Netherlands*

Case Report

A 69-year-old man presented with the sudden development of a pale, painful and pulseless left lower leg. Physical examination revealed a varicocele on the left side which had apparently been present for only a few months. There was no history of intermittent claudication. Chest X-ray showed multiple lesions, suggesting metastases in both lungs. Embolectomy under local anaesthesia was performed immediately. Microscopic examination of the thrombus showed tumour cells. Subsequent analysis showed renal function to be abnormal and an intravenous urogram showed a picture suggestive of left renal carcinoma. Surgical resection was not attempted. The patient's general condition deteriorated rapidly and he died 23 days after admission. Autopsy demonstrated a large renal carcinoma with pulmonary metastases and invasive growth in the renal vessels, inferior vena cava and left ureter.

Comment

Malignant tumour emboli to peripheral arteries are relatively rare and most of them originate from lung tumours (Starr *et al.*, 1981). Until now only one renal carcinoma presenting with peripheral arterial occlusion has been described (Stanley and Eto, 1978). Renal carcinomas are known to present with protean manifestations (Chisholm, 1974); the present case stresses the diversity of symptoms of the disease. The sudden occurrence of peripheral emboli without a history of claudication or cardiac arrhythmia should raise the suspicion of malignancy; further analysis may be decisive for subsequent treatment. However, this diagnostic clue is probably of no prognostic value for the patient as it concerns a late symptom of disseminated disease. It is important to undertake microscopic examination of thrombus material removed after embolectomy.

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Requests for reprints to: Dr. G. J. C. M. Niessen, Department of Surgery, St. Lambertus Hospital, P.O. Box 98, 5700 AB Helmond, The Netherlands.

Carcinoma of the Seminal Vesicle

J. J. LANGHAM-BROWN and G. F. ABERCROMBIE, *Department of Urology, St Mary's Hospital, Portsmouth*

Case Report

A 21-year-old man was admitted with acute retention of urine due to blood clots. He had had three episodes of haematuria and haematospermia in the preceding 8 weeks. Nine months previously he had noticed an episode of urethral discharge.

Intravenous urography was unremarkable. Urine cultures, including examination for acid fast bacilli, were normal. Blood count and screening tests for venereal disease were also normal. At cystoscopy the bladder was normal. A mass above and to the left of the prostate was felt on bimanual examination. A diagnosis of inflammatory disease was made and the patient discharged on antibiotics.

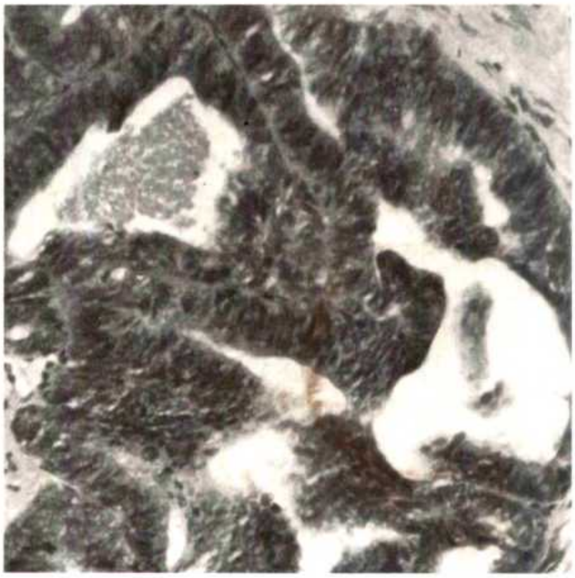

Fig. Trucut biopsy showing tall columnar cell carcinoma of seminal vesicle with poorly defined intraluminal papillae. (H and E × 200).

He was readmitted 6 weeks later with a further acute episode. IVU showed bladder displacement and examination under anaesthesia revealed that the mass had increased in size. Transrectal biopsy, using a Trucut needle, was carried out. Histology showed a moderately differentiated papillary carcinoma of the seminal vesicle, with stromal invasion. There was no prostatic tissue present.

He was treated with megavoltage radiotherapy. A year later widespread pulmonary metastases and a lytic lesion in the left femur appeared. In spite of intensive chemotherapy (vincristine, 5FU, methotrexate and cyclophosphamide) his disease progressed and he died 3 years later.

Comment

Dalgaard and Giertsen (1956) accepted as proven only 23 of 34 cases of carcinoma of the seminal vesicles reported in the literature to that date. Awadalla *et al.* (1968) and Goldstein and Wilson (1973) reported a further two cases.

These authors highlighted the difficulty of distinguishing carcinoma of the seminal vesicle from prostatic disorders. Our patient was a young man and was originally thought to have inflammatory disease. Transrectal biopsy established the diagnosis.

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Requests for reprints to: G. F. Abercrombie, Department of Urology, St Mary's Hospital, Milton Road, Portsmouth PO3 6AD.

Testicular Infarction in a Patient with Sickle Cell Trait

G. H. URWIN, N. KEHOE, S. DUNDAS and M. FOX,
Department of Urology, Royal Hallamshire Hospital, Sheffield

Case Report

A 20-year-old male negro was admitted with a 2-week history of an initially painful swelling of the right side of the scrotum. There was no history of trauma, urinary symptoms or urethral discharge and his general health was good. Examination revealed a normal left testis but the right one was enlarged to about twice the normal size, not tender and the spermatic cords were normal.

Investigation revealed normal haematological and biochemical indices. He was HbS positive and subsequent haemoglobin electrophoresis was consistent with sickle cell trait. Abdominal and testicular ultrasound revealed normal para-aortic nodes and the right testis showed loss of normal architecture, this being replaced by smooth, featureless tissue suggestive of tumour.

The right testis was explored through an inguinal approach after clamping the cord near the internal inguinal ring. The testis was found to be markedly adherent to the scrotum and some difficulty was experienced in its mobilisation. The gonad was obviously abnormal and was therefore excised.

Pathological examination showed an infarcted testis with a thick capsule of reactive vascular fibrous tissue (Fig. 1). The capsule measured 4 mm in thickness; the presence of mature collagen may be indicative of previous episodes of ischaemia. The vessels of the spermatic cord were occluded by thrombus containing sickled red cells (Fig. 2).

Comment

Infarction of organs such as brain, heart, spleen, bone marrow, placenta, bone and spinal cord are well documented in association with sickle cell syndrome (Wintrobe, 1974). We believe this to be a unique association of testicular infarction in an individual with sickle cell trait.

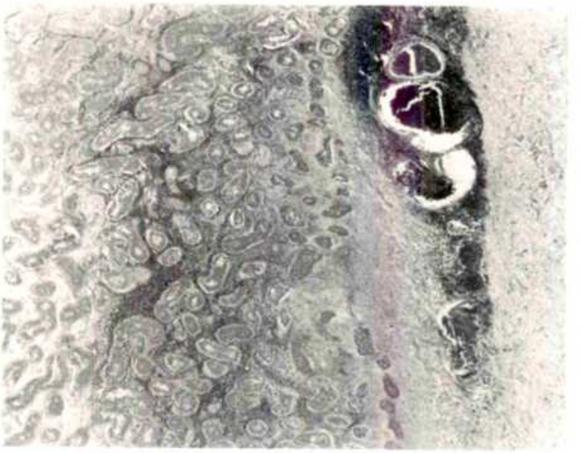

Fig. 1 Infarcted seminiferous tubules, thrombosed blood vessels and a markedly thickened fibrous tissue capsule. (H and E × 10).

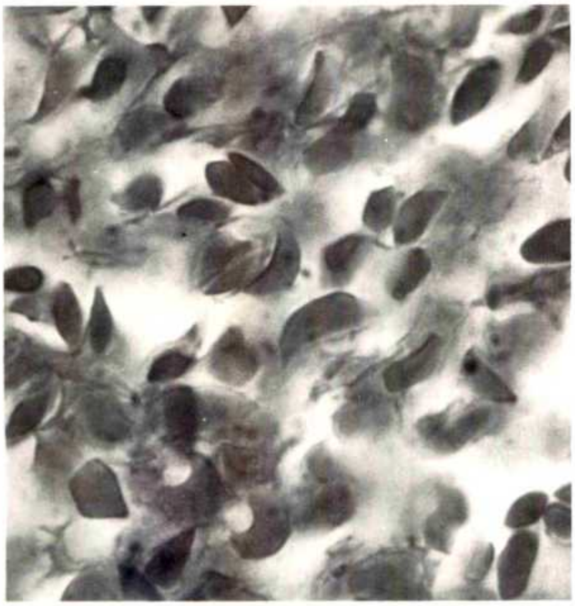

Fig. 2 The thrombosed blood vessels contain fragmented and sickled red blood cells. (H and E × 1000).

Reference

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Requests for reprints to: G. H. Urwin, Department of Urology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF.

Carcinoma of the Colon as a Late Complication of Ureterosigmoidostomy

G. H. URWIN and J. L. WILLIAMS, *Department of Urology, Royal Hallamshire Hospital, Sheffield*

Case Report

This male patient was born in 1949 with exstrophy of the bladder. Bilateral ureterosigmoidostomy was performed at 3 months of age and cystectomy at the age of 2. At the age of 33 he was referred with uraemia and a metabolic acidosis. An intravenous urogram revealed bilateral hydronephrosis and hydroureter (Fig. 1). Flexible sigmoidoscopy revealed two polypoid lesions in the colon at 40 and 29 cm, biopsy of the upper lesion showing severely dysplastic epithelium, the lower showing normal colonic mucosa.

Laparotomy revealed an obvious tumour 2 cm in diameter at the site of the left ureterocolic anastomosis and a smaller tumour at the site of the right (corresponding to 40 and 29 cm respectively). Sigmoid colectomy with end-to-end colonic anastomosis was performed with diversion of the ureters into an ileal conduit brought out into the left iliac fossa.

The resected specimen showed a polypoid mass arising at both ureterocolic anastomoses (Fig. 2). Sections of the

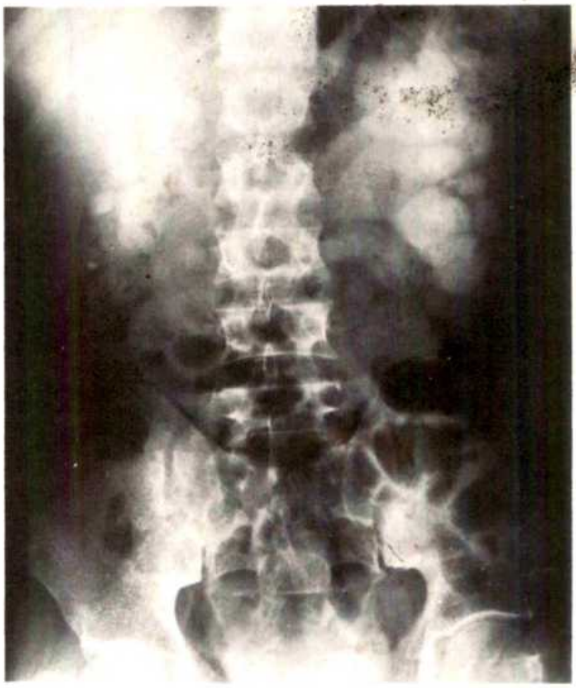

Fig. 1 Intravenous urogram showing bilateral hydronephrosis and hydroureter.

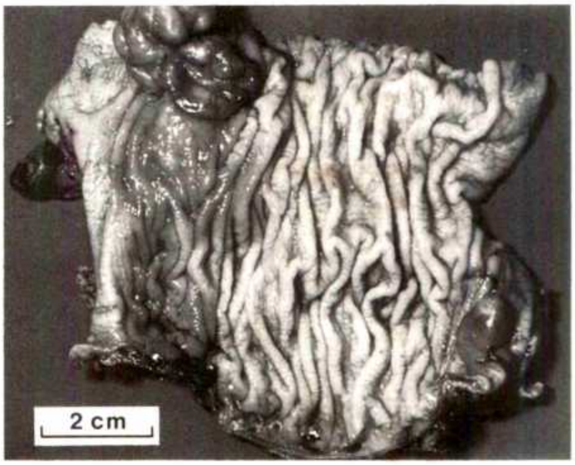

Fig. 2 Operative specimen showing polypoid lesions arising at both ureterocolic anastomoses.

upper lesion showed a well differentiated carcinoma arising at the junction between the transitional and glandular epithelium, invading muscle but not extending through the bowel wall. The lower tumour consisted of oedematous stroma and proliferative blood vessels only.

Comment

Since the first report by Hammer (1929) of a colloid carcinoma of the colon developing in a 60-year-old man 10 years after ureterosigmoidostomy for exstrophy of the bladder, over 50 further patients have been described (Charron and Delisle, 1982).

We report a further patient who developed a carcinoma of the colon 33 years after ureterosigmoidostomy for exstrophy of the bladder.

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Requests for reprints to: G. H. Urwin, Department of Urology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 5JF.

Primary Signet Ring Cell Adenocarcinoma of the Urinary Bladder with Calculi

P. V. N. KUMAR, A. YOUSSEFI and A. AHMAD,
Departments of Pathology and Urology, Shiraz University Medical School, Shiraz, Iran

Adenocarcinoma of the bladder is a rare tumour which comprises less than 2% of all bladder malignancies (Thomas *et al.*, 1971). The signet ring type of adenocarcinoma is even more uncommon and less than 10 well documented cases have been reported in the literature (Mostofi *et al.*, 1955; Poore *et al.*, 1981). These tumours are usually recognisable grossly as foci of mucosal thickening or as an exophytic mass and morphologically are identical to signet ring cell carcinomas of the gastrointestinal tract, breast and nasal cavity. Adenocarcinoma of the bladder has a poor prognosis with early penetration of mucosa, submucosa and muscularis.

A case of primary signet ring cell adenocarcinoma of the bladder associated with multiple stones has not, to our knowledge, been reported previously.

Case Report

A 40-year-old male came to Nemazee Medical Emergency Ward on 22 April 1984 complaining of fever with chills. Respirations were rapid, with Kussmaul breathing, and there was an increase in blood urea nitrogen (200 mg%) and creatinine (14.8 mg%). Plain abdominal X-ray showed multiple bladder stones. Chest X-ray was unremarkable.

On 1 May 1984 the patient was transferred to the Urology Department for lithotomy and during operation a bladder tumour was found. Biopsy showed it to be a signet ring adenocarcinoma. Three large calcium and phosphate stones were removed (Fig.). Post-operative radiological investigation failed to reveal any evidence of gastro-intestinal malignancy. The patient's condition deteriorated and he died of sepsis on the 35th post-operative day. An autopsy was performed.

Pathological Findings

Gross: at autopsy, a 5 × 4 cm polypoid nodular tumour mass with a mucoid external surface was seen occupying the trigone of the bladder and occluding both ureteric orifices (Fig.). The dome and the anterior wall were tumour-free and there was no extravesical extension of tumour tissue. There was no evidence of malignancy in the gastrointestinal tract.

Microscopy

Multiple specimens were taken from the tumour mass at autopsy. The tumour was made up chiefly of signet ring cells, sheets of which were seen infiltrating the lamina

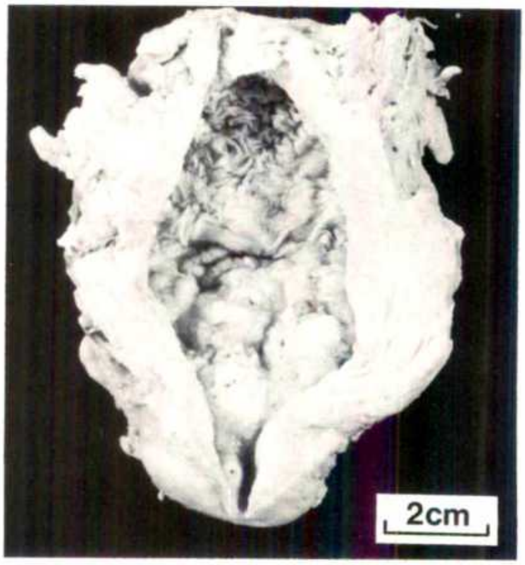

Fig. Post morten specimen showing a polypoid mass at the base of the urinary bladder.

propria. The individual cells were large and polygonal, with pleomorphic, hyperchromatic nuclei that frequently were displaced by a single prominent intracytoplasmic vacuole which stained positively for mucin. The surface epithelium showed transition to malignancy and well formed malignant glandular structures were seen. Brunn's nests and cystitis glandularis glands were also present and sometimes showed evidence of anaplasia. There was also focal squamous metaplasia of the surface epithelium. A specimen of the rectal mucosa was negative for malignancy.

Comment

Transitional epithelium has the ability to transform into squamous and glandular epithelium in response to a variety of stimuli, such as calculi and chronic infection, and metaplasia is also seen in the exstrophied bladder.

Primary adenocarcinoma of the bladder is a rare tumour which can arise from either a urachal rest or from metaplastic bladder mucosa. In the present case the basal situation of the tumour and the microscopic finding of cystitis glandularis and squamous metaplasia, with a transition of the surface epithelium to malignancy, indicate an origin from metaplastic epithelium rather than from the urachus. Interestingly, the tumour is associated with multiple stones, which also favours a vesical origin. It is generally accepted that adenocarcinoma of the bladder has a poor prognosis, Mostofi *et al.* (1955) reporting a 33% 5-year survival rate.

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Requests for reprints to: P. V. N. Kumar, Department of Pathology, Shiraz University Medical School, Shiraz, Iran.

British Journal of Urology (1986), **58**, 344

Point of Technique

A Simple Approach to the Entire Urethra

W. A. DE SY, A. VERBAEYS, R. ROELANDT and W. OOSTERLINCK, *Department of Urology, University Hospital, Gent, Belgium*

Very long strictures were encountered in 5% of cases in a series of more than 100 free full thickness skin graft urethroplasties.

For penile strictures the skin of the penis is sleeved down towards the base of the penis. For strictures at the bulbous urethra an inverted U-shaped perineal incision is preferred.

To expose the complete urethra in patients with very long strictures, sometimes involving the whole urethra, we circumcise the patient and dissect the preputial skin spirally in order to obtain a graft of sufficient length (Fig. 1). We then sleeve down the penile shaft as far as the base of the penis (Fig.2), make an inverted U-shaped perineal incision and continue the dissection distally so that the penis can be completely detached and brought out of the wound (Fig. 3). After repair of the stricture according to the method described by Devine *et al.* (1963), the penis is brought out of the scrotal tunnel into its skin sleeve. The circumcision and perineal incision are closed.

We have found that this approach causes no problems other than those usually encountered with wounds in this part of the anatomy (De Sy and Oosterlinck, 1981; De Sy *et al.*, 1981).

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De Sy, W. A., Oosterlinck, W. and Verbaeys, A. (1981). European experience with one-stage urethroplasty with free full thickness skin graft. *Journal of Urology*, **125**, 502-503.

Requests for reprints to: W. A. De Sy, Department of Urology, Akademisch Ziekenhuis, De Pintelaan 185, B-9000 Gent, Belgium.

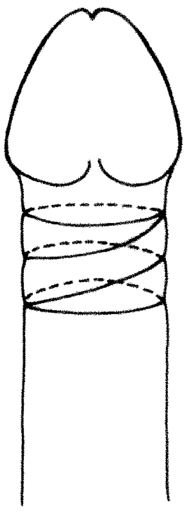

Fig. 1

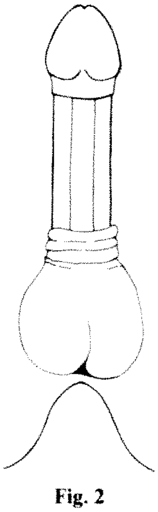

Fig. 2

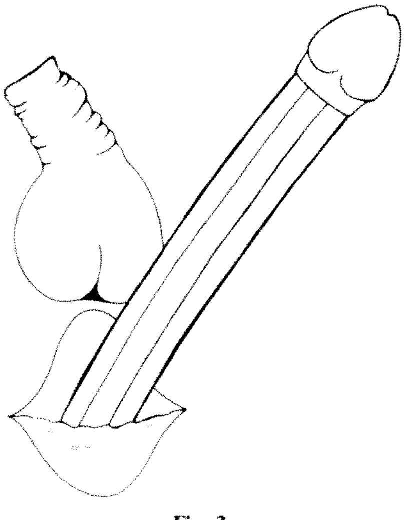

Fig. 3

Fig. 1 The spiral preputial incision yields a free full thickness skin graft of sufficient length. Fig. 2 The penile skin is sleeved down to the base of the penis. The perineal incision has the shape of an inverted U. Fig. 3 The penis is completely denuded.

British Journal of Urology (1986), **58**, 345

Notices

British Association of Urological Surgeons and Canadian Urological Association

Presidents: Professor J. P. Blandy, MA, DM, MCh, FRCS, FACS
Dr G. A. Farrow, MD, FRCS(C), FACS

Annual Meeting: London, 17-20 June 1986

All correspondence to: R. G. Notley, MS, FRCS, Honorary Secretary, British Association of Urological Surgeons at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Surgitek Prize for Urology 1986

The award has been made to Mr R. S. Kirby for his submitted paper entitled "Urethrovesical dysfunction in progressive autonomic failure with multiple system atrophy."

Shackman Travelling Fellowships 1987

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited Training Programme in Urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent University status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to Urology or to Renal Transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1986.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

Sixth International Congress of Cryosurgery

Athens, Greece. 4-6 September 1986

Further information from: Professor C. Dimopoulos, Sismanoglion Hospital, Maroussi, Athens, Greece.

International Symposium on Transrectal Ultrasound in the Diagnosis and Management of Prostate Cancer

Detroit, USA. 11/12 September 1986

Further information from: J. Dowty, Department of Radiology, Catherine McAuley Health Center, P.O. Box 995, Ann Arbor, Michigan 48106, USA.

First Symposium on Morphological Basis of Human Reproductive Function

Fiugge Terme, Italy. 11-12 September 1986

Further information from: Professor G. Spera, V Clinica Medica, Policlinico Umberto 1, Università "La Sapienza", 00161 Rome, Italy.

Fourth World Congress on Endourology and ESWL

Madrid, Spain. 11-13 September 1986

Further information from: General Secretariat, Ultramar Express, S.A., Congress Department, Santiago Bernabeu 16, 28036 Madrid, Spain.

International Society for Dynamics of the Upper Urinary Tract

Newport, USA. 14-16 September 1986

Further information from: Dr B. L. R. A. Coolsaet, Noordheuvel 50, 2170 Wuustwezel, Belgium.

42nd Congress of Swiss Association of Urology

Luzern, Switzerland. 18-20 September 1986

The following topics will be discussed:

Hypospadias
Disturbances of bladder function (together with Swiss Society of Pediatric Surgery)
The septic patients (together with Swiss Society of Surgery)
Free communications

Further particulars from: Professor K. Bandhauer, Klinik für Urologie, Kantonsspital, CH-9007 St. Gallen, Switzerland.

Sixth Copenhagen Symposium on Endoscopic Urological Surgery

Herlev, Denmark. 27-30 January 1987

Further information from: F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.

British Journal of Urology (1986), **58**, 346-348

Book Reviews

Urodynamics. Principles, Practice and Application. Edited by A. R. Mundy, T. P. Stephenson and A. J. Wein. Pp. xv + 394. Edinburgh: Churchill Livingstone. 1984. Price £35.00.

This book represents the combined work of no less than 28 different contributors jointly edited by three urologists whose expertise in the management of idiopathic and neurogenic vesico-urethral dysfunction is widely appreciated.

The 394 pages of text offer a comprehensive guide to the investigation of functional disorders of the lower urinary tract with a commendable bias towards the practical problems that can often arise, even in the most experienced hands. The initial section, which presents current views on the clinical anatomy and physiology of bladder and urethral function, is surprisingly detailed for a book of this size, although the reviewer suspects that many readers may not entirely agree with some of the views expressed therein. The remaining six sections provide a detailed evaluation of urodynamics in current urological practice. This provides an invaluable source of information on patient selection, methodology and interpretation of results for those urologists and allied medical personnel whose experience in urodynamics is limited. Conversely, even the most experienced urologist will appreciate the clarity with which each section is presented and the manner in which the role of urodynamics is evaluated in various dysfunctional states.

A good textbook will stimulate and satisfy a reader's curiosity and this book certainly does both. It is reasonably priced and is strongly recommended to medical personnel of all grades and disciplines whose practice involves the investigation and treatment of lower urinary tract dysfunction.

The Urinary Tract and the Catheter. Infection and Other Problems. By N. Slade and W. A. Gillespie. Pp. x + 126. Chichester: Wiley. 1985. Price £17.00.

This compact book is the product of Bristol and Dublin, presenting personal contributions covering 30 years of interest in the urinary tract and the catheter and paying particular attention to contributions from 1980 to 1984. There is a brief but very interesting historical survey, followed by a study of microbiology, antibiotics and laboratory investigation leading to the consequential effects of infection. The analysis on prevention or urinary infection is practical, stressing the importance of "good urological housekeeping"! In the chapter on catheterisation and the use of drainage equipment a bewildering choice is given and mention is made of the importance of costing (a matter which is often not taken into adequate consideration).

The closing chapters are essentially practical and are presented completely and simply, with instructions on hygiene in managing the patient in the ward and a case at home. Each chapter is followed by a full and adequate list of references.

This book is recommended since it achieves its aims, which are to impart specific knowledge to doctors and nurses in order to improve, if not to save, the lives of many of the patients. This book should be available in all urological units, both for reading and as a reference source.

Interventional Ultrasound. Edited by H. H. Holm and J. K. Kristensen. Pp. 186. Copenhagen: Munksgaard. 1985. Price D.kr. 300.00.

First there was interventional radiology; now there is interventional ultrasound. Ultrasound has always looked promising as a potential aid to interventional procedures requiring accurate knowledge of depth within tissue, a parameter which conventional X-ray apparatus is unable to provide. A Danish urologist, Hans Holm, appreciated this fact over 15 years ago and having used ultrasound to guide renal cyst punctures, he extended his sphere of activity and now heads one of the largest and most prestigious interventional laboratories in the world. The Copenhagen story is second to none and contained in the pages of this small book is a concise account of Holm's experience supplemented, when necessary, by that of other experts in the field.

All aspects of interventional ultrasound are covered, including urological procedures from simple cyst puncture to percutaneous nephrolithotomy and guided prostatic biopsy.

The growing field of percutaneous fine needle aspiration biopsy is well covered, with much attention being paid to equipment, technique and preparation and handling of material. There is a section dealing with obstetric applications and an interesting chapter on fetal therapy. By far the commonest correctable fetal abnormalities occur in the renal tract. Interventional echocardiography is discussed and an important chapter gives detailed consideration to the hazards of fine needle aspiration biopsy and concludes that there are few.

This is an excellent little book, bristling with useful information and clearly set out. A urologist can become an interventional expert overnight!

Radiology of the Kidney. By A. J. Davidson. Pp. xix + 703. Philadelphia: Saunders. 1985. Price £98.00.

It is not long since I reviewed another uro-radiology volume written almost exclusively by a single author, and one cannot but admire Dr Davidson's achievement in producing all but 40 pages of this 700-page work confined solely to the radiology of the kidney.

Part I deals with technique and anatomy and lacks balance, allotting less than a page each to ultrasound, CT scanning and angiography while devoting whole chapters to radionuclide imaging and interventional radiology. Part II, entitled The Renal Parenchyma, accounts for almost half of the book, and Part III covers the pelvicaliceal system. The chapter headings in Parts II and III are dictated by the effects of pathology on renal morphology, thus dividing them into what the author terms "Diagnostic Sets", *i.e.* small scarred unilateral kidney, small smooth bilateral kidneys and so on. This logical way of looking at the upper renal tract should appeal to urologists as much as radiologists. Unfortunately, all that needs to be said about the kidney does not fall conveniently into this format. In order to cope with some miscellaneous and unconnected topics Part IV employs a different approach. Entitled "Essays", it guides us through such disparate areas as the nephrogram, renal failure and renal masses, angiography (again), the retroperitoneum and renal trauma.

If one believes, as one should, that the IVU remains the single most informative radiological assessment of renal pathology, this book has much to offer with its wealth of high quality photographs and clear format. Concise summaries appear at the end of each section and the bibliography is extensive and well set out.

As a standard reference to renal diagnosis this book may seem at first to lack balance between classic radiology and the new technologies. Appearances are, however, deceptive and it is merely the novel approach that creates the illusion.

Atlas of Male Reproductive Pathology. (Current Histopathology Series, Volume 10). By I. D. Ansell. Pp. 83. Lancaster: MTP Press. 1985. Price £57.95.

This is one of a series of high quality colour atlases on histopathology under the general editorship of Professor G. A. Gresham. This book, confined to the pathology of the male genital system, contains colour photos (mainly photomicrographs) which are generally good. There are a few exceptions where the colours appear rather pale. These are mainly photos of low magnification which are in any case difficult to reproduce satisfactorily.

Nevertheless the subjects are well covered and each section or chapter is accompanied by a discussion of the conditions depicted. This is useful and well presented. The author favours the British classification of testicular tumours but refers also to the equivalent category in the WHO system. There is a useful discussion of the rare forms of prostatic tumour, including adenocarcinoma of ductal origin, which includes the somewhat controversial entity endometrioid carcinoma. Inflammatory conditions are well covered and include most of the conditions likely to be encountered in clinical practice.

Unfortunately pages 17 to 32 were missing from the review copy!

Invasive Uroradiology. By M. K. Elyaderani, S. J. Kandzari, W. R. Castaneda and P. H. Lange. Pp. vii + 250. Lexington, Toronto: Collamore Press. 1984. Price £43.35.

Interventional radiology is now accepted as an established and fast growing subspecialty, tailor made to appeal to any ambitious but frustrated surgeon turned radiologist. All systems are now open to a variety of techniques but the widest application probably lies in the urinary tract. The radiologist has for a long time happily drained renal cysts but the last few years have seen the rapid expansion of many other diagnostic and therapeutic interventional procedures made possible with the assistance of newer imaging modalities, namely CT and particularly ultrasound.

A great deal of information may be gleaned from a host of urological and radiological journals but here we have a compact and comprehensive review of the subject skilfully put together by a group of experts from both specialties working in concert in the USA. Above all, this book stresses the growing importance of the urological/radiological interface and the co-operation so vital to successful interventional diagnosis and treatment. All endourological procedures are covered in detail, including paediatric and open intra-uterine applications. The approach is essentially practical, the concise text being extensively illustrated with radiographs, rather indifferent ultrasonic images (some of which are published upside down) and numerous excellent line drawings. There are many useful references.

Although techniques are changing daily, this book provides a good basic approach to the whole subject and its content is a must for urologists and radiologists in training. It is rather expensive for the individual to buy but should be in the departmental library.

Microbial Diseases in Nephrology. Edited by A. W. Asscher and W. Brumfitt. Pp. xviii + 366. Chichester: Wiley. 1986. Price £35.00.

This book is the Proceedings of the Third National Symposium on Microbial Disease in Nephrology, held in London in March 1985. The emphasis of the 21 contributions is on those bacterial infections which have a direct invasive effect on the urinary tract. There are several important contributions on the assessment and significance of overt and covert urinary tract infections; a chapter on the place of a urinary infection clinic as well as useful contributions on such important topics as infections in childhood, peritonitis in CAPD and infections in renal transplantation are included. The chapter on urethral catheterisation would have been all the more useful if the comments had been extended to include urethral instrumentation, for this topic still occupies the minds and time of many urologists. There is one chapter on the use of antibiotics in urinary tract infections and this is a valuable but cautionary review that attempts to guide the readers into thinking more carefully about the cost effectiveness of their prescribing.

The Kidney. By H. E. de Wardener. Fifth edition. Pp. x+604. Edinburgh: Churchill Livingstone. 1985. Price £25.00.

A fifth edition of this book, especially after an interval of 12 years since the fourth edition, is worthy of comment. Emeritus Professor de Wardener has after many years been able to maintain an excellent balance between the encyclopaedic, multi-author book and the pocket book. However, it has, over the years, doubled its size and this reflects the inevitable growth of this subject. The essential feature of this book is its readability and this edition brings it right up to date once more. This is a book that will appeal to many members of the profession but it will also be a useful companion amongst urology books, giving ready access to many nephrological topics that are of relevance to urologists.

Atlas of Glomerular Disease. Morphological and Clinical Correlation. By Priscilla Kincaid-Smith, J. P. Dowling and D. C. Matthews. Pp. vii+86. Sydney: ADIS Health Science Press. 1985. Price £27.00.

The aim of the book is to provide a pictorial representation of glomerular disease, correlating these with the clinical presentation. The book is meant to assist both renal physicians and pathologists in their understanding of these diseases.

The value of an atlas stands or falls on the quality of the illustrations. These are certainly adequate, although there is perhaps an undue preponderance of electronmicrographs and photomicrographs of sections stained by the silver methenamine method. This leads to a rather unbalanced presentation.

The text is extremely brief but is clear and straightforward. There is nothing on the haemolytic uraemic syndrome, although it appears in the index. There is a brief list of references—several of these refer to papers by the senior author.

There are some very fine publications covering this subject and it is doubtful if this one has anything extra to offer which has not already been done as well, if not better. This book will be of limited interest to the readers of this Journal.

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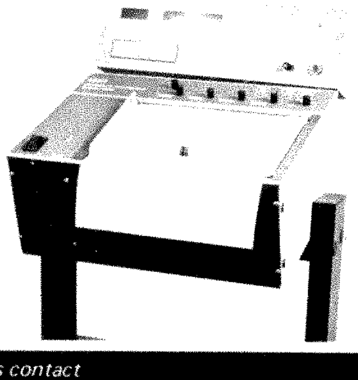

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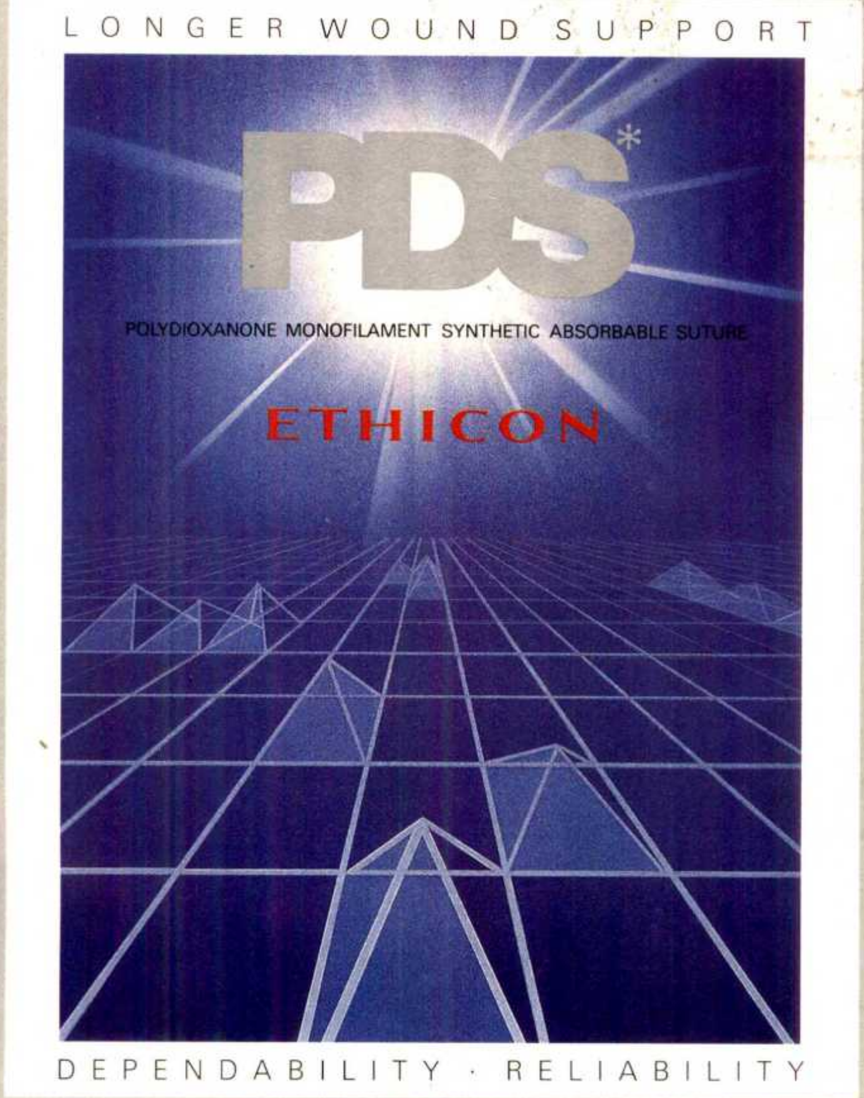
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TECHNICAL DATA
DATA SHEET

PDS* (Polydioxanone)
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Presentation

PDS (Polydioxanone) Monofilament Synthetic Absorbable Suture is prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding D & C blue No 6 (gauge 0.2 metric and 0.3 metric) D & C violet No 2 (gauge 0.4 metric to 5 metric) during polymerisation. These sutures may also be manufactured undyed (clear).

PDS (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action

Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second, absorption rate or loss of mass.

Data obtained from implantation studies in rats show that, at two weeks post implantation, approximately 70% of the suture strength is retained whilst at four weeks the strength retention is approximately 50%. At eight weeks approximately 14% of the original strength remains. *This indicates a significantly longer period of wound support than previously available with an absorbable suture.*

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within six months.

Uses

PDS (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration

By implantation.

Contra-indications, Warnings, etc.

These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal mucosal sutures could cause localised irritation if left in place for longer than 10 days and should be removed as indicated. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

The safety and effectiveness of PDS (Polydioxanone) sutures in neural and cardiac tissue have not yet been established. The use of this material in the renal tract is currently under investigation.

Pharmaceutical Precautions

Do not resterilise.

Legal Category P

Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Packaging

The gauge range available will be 0.3 metric (9/0) to 5 metric (2). Various lengths of material attached to non traumatic stainless steel needles are packaged in sealed aluminium foil sachets.

The primary pack is contained in a peel-apart secondary pouch and contained in a film-wrapped drawer style carton.

Further Information

No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos PL 0508/0011 (dyed);
PL 0508/0012 (clear).

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